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# NASEEM SHERZAD FCPS-1 HIGH-YIELD

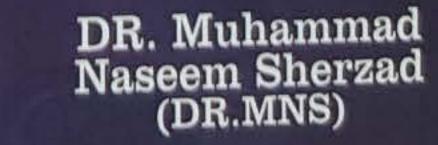


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# NASEEM SHERZAD FCPS=1 HIGHYIELD

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By

Dr. Muhammad Naseem Sherzad (Dr.MNS)

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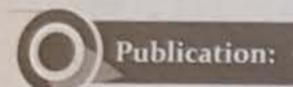




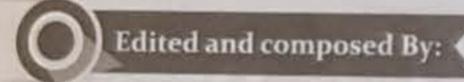


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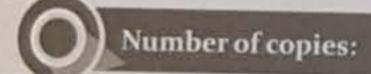
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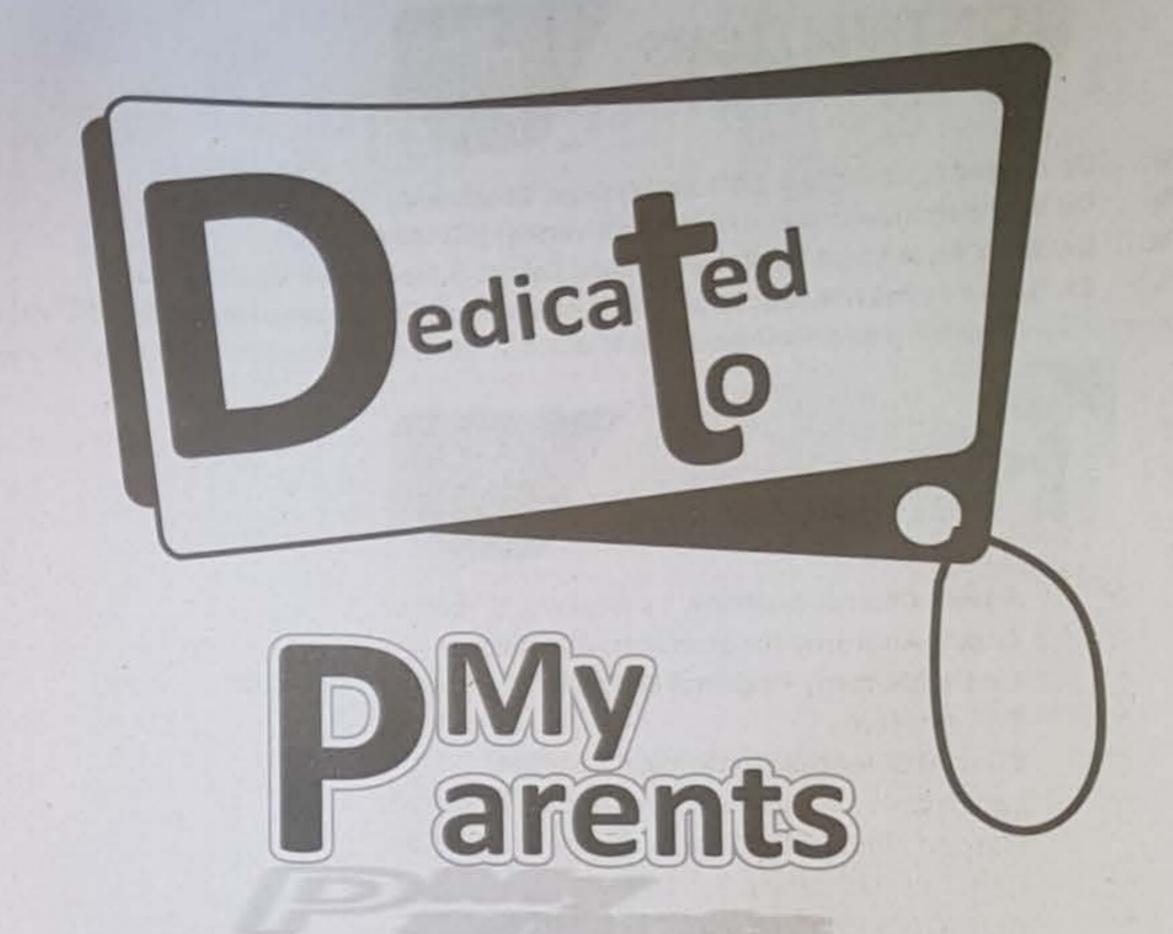
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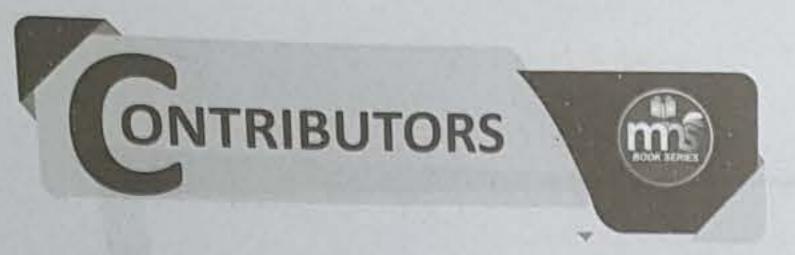
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My Sweet Brothers

- Idrees Sherzad
- Naeem Sherzad and
- My Guide, My Uncle Dr. Pushtoon Sherzad

Who has always encouraged me.



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# Preface



The only leader to success is hard work. There is no shortcut to the process of learning. The purpose of this book is to stimulate the latent curiosity for more knowledge.

Honestly speaking, we are tired of so many books that are being used for FCPS part I and other post-graduate exams; moreover, there were so many mistakes in most of the books with the exception of few that I felt the urge to write something, which should be almost error free. No errata shall be needed for this book and there shall be no need to study BCQ's and theory books seperately because this book is written in such a format that everything is given under single topic for example under topic of liver, the anatomy, physiology, pathology, histology, embryology, pharmacology, tricky points and clinical points regarding liver have been illustrated. The aim of this book is to cover each and every mcqs in depth, while understanding the concept and to correlate various tricky points at the same time.

Different people have different goals and thoughts: but to those who are planning to practice in Pakistan as a doctor, one has no choice but to do FCPS, MD, MS (JCAT exam for MD/MS) and for Pakistani nationals who have graduated from abroad it is very challenging to clear all the steps of PMDC exams without proper guidance. This book has been written with the aim to help these doctors and medical students and provide them with a quick and easy review of the basic subjects that may come up in the various exams mentioned above.

Work hard, repeat one thing many times, that is how it stays in the mind for longer. As great saying by Bruce Lee goes "I fear not the man who has practiced 1000 kicks once, but I fear the man who has practiced one kick 1000 times.

By no means it is perfect and there may be some ambiguity in the text. I have tried my best to solve them accurately to the best of my knowledge and ability. However, there may be possibility of human or computer error. Readers are encouraged to come forth with suggestion and correction. Your suggestion and positive criticism are always welcome to improve the standard of this book. You can also join me on FACEBOOK at this link. facebook.com/mohdnaseem.qarar or /sherzadbook.

Dr. Muhammad Naseem Sherzad
Email: mnaseem2015@gmail.com



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- O) ANATOMY
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NASEEM SHERZAD FOPS - HIGH-VIELD

CHAPTER

1

# UPPER LIMB

#### **Bones and Joints**

#### ....

#### Clavicle

- It is also called Collar or beauty bone
- The clavicle provides osseous continuity between the upper limb and thorax.
- Given its relative size and the potential forces that it transmits from the upper limb to the trunk, it is not surprising that it is often fractured. The typical site of fracture is the middle third. The medial and lateral thirds are rarely fractured.
- It is the first bone to ossify in intrauterine life.
- It is the only long bone that is placed horizontally in the body. It is modified long bone
- Although It is a long bone, but it ossify mostly from the membrane
- The most common type of bone fracture during delivery and labor is a clavicle fracture
- It is the <u>most commonly fractured bone in the body</u>. The fracture usually occurs as a result of a fall on the shoulder or outstretched hand. The force is transmitted along the clavicle, which breaks at its weakest point, the junction of the middle and outer thirds. (Reference: SNELL 8<sup>th</sup> edition P.433)

#### Scapula

- The scapula is a large flat triangular bone and resides over the posterior surface of ribs 2 to 7.
- Scapula attach to the thoracic wall by Serratus anterior muscle, injury to this muscle or its nerve supply will cause winging scapula. The Inferior angle of the scapula is located at the level of T7.
- From infraglenoid tubercle, the long head of the triceps brachii muscle originates while from supraglenoid tubercle the long head of the biceps brachii muscle originates.
- In Case of fracture of coracoid process of scapula damage to Pectoralis Minor Muscle occurs.
- Important differences:
  - ✓ The distance by which two touch stimuli must be separated to be perceived as two
    separate stimuli is greatest on the back of the scapula
  - ✓ Two-point discrimination is high at fingertip and lips and lowest at back
  - ✓ In two-point discrimination, the mechanism involved is lateral inhibition (increase contrast between the active receptive field and the inactive neighbors)

Chapter 1

#### Bone of Hand

- The eight carpal bones are the bones of the wrist;
- The five metacarpals are the bones of the metacarpus.
- The phalanges are the bones of the digits-the thumb has only two, the rest of the digits have three

#### Carpal Bone

#### She Looks Too Pretty, Try To Catch Her

#### Proximal row: She Looks Too Pretty

- From lateral to medial and when viewed from anteriorly, the proximal row of bones consists of:
  - √ The boat-shaped Scaphoid
  - ✓ The Lunate, which has a 'crescent shape'
  - √ The Three-sided Triquetrum bone
  - √ The Pea-shaped Pisiform

#### Specific features:

- ✓ The pisiform is a sesamoid bone in the tendon of flexor carpi ulnaris and articulates with the anterior surface of the triquetrum. The ulnar nerve and artery lie adjacent to the pisiform bone
- ✓ The scaphoid has a prominent tubercle on its lateral palmar surface that is directed. anteriorly
- The commonest carpal injury is a fracture across the waist of the scaphoid bone and the commonest complication of scaphoid bone fracture is non-union (nonunion > avascular necrosis)
- In approximately 10% of individuals, the scaphoid bone has a sole blood supply from the radial artery, which enters through the distal portion of the bone to supply the proximal portion. When a fracture occurs across the waist of the scaphoid, the proximal portion therefore undergoes avascular necrosis owing to the retrograde blood supply.

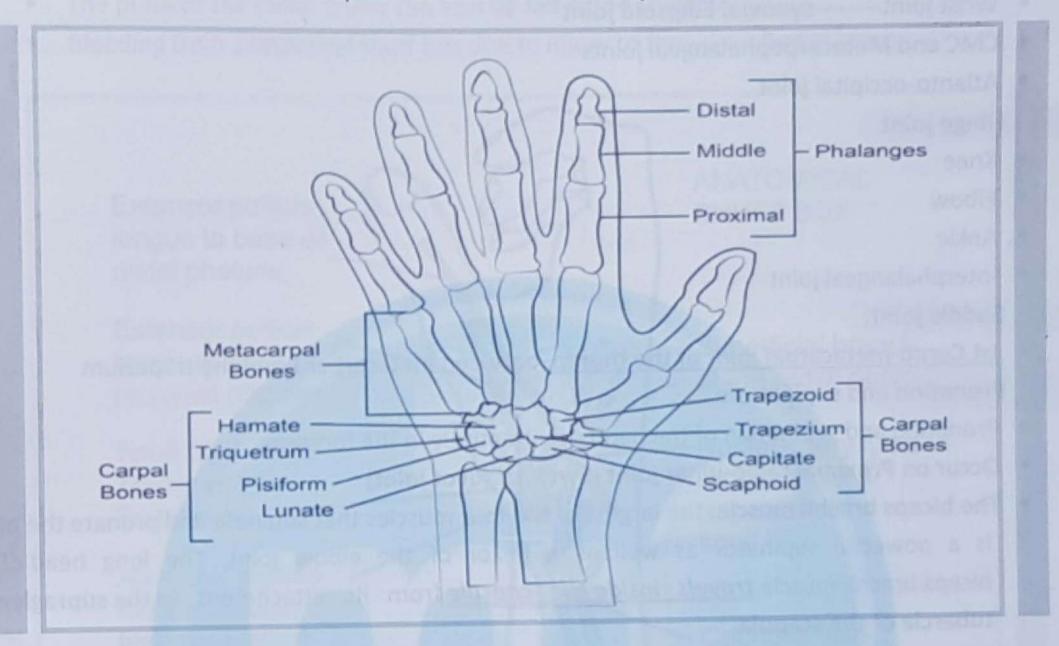
#### Distal row: Try To Catch Here

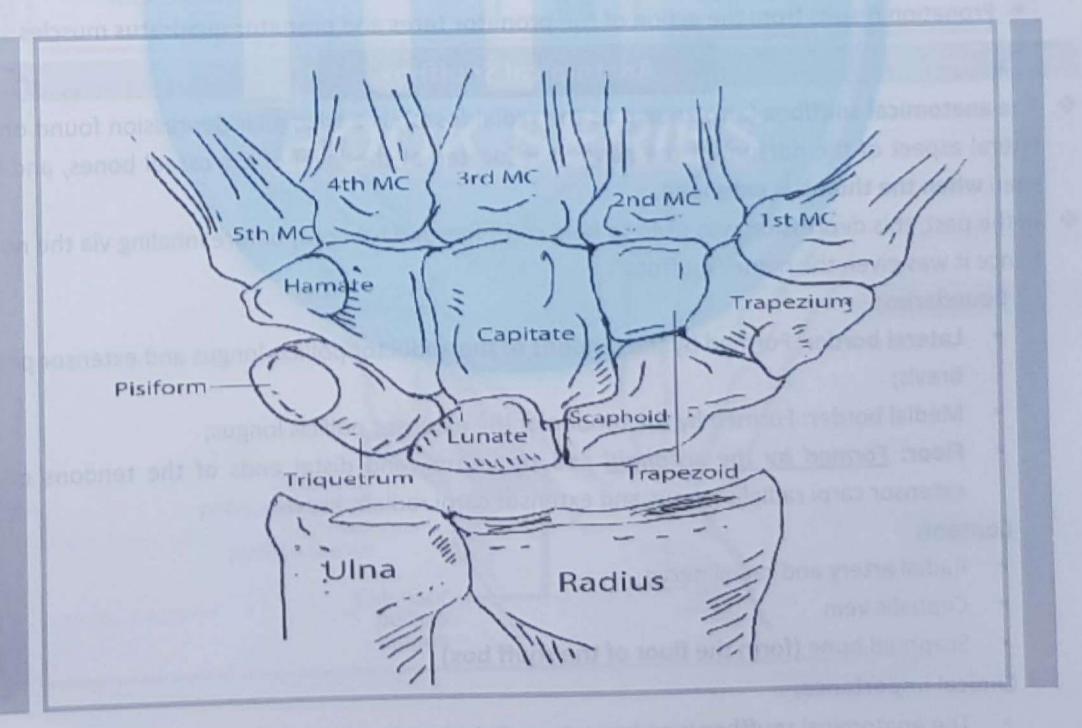
- \* From lateral to medial and when viewed from anteriorly, the distal row of carpal bones consists of:
  - ✓ The irregular four-sided Trapezium bone
  - ✓ The four-sided Trapezoid
  - ✓ The Capitate, which has a head
  - ✓ The Hamate, which has a hook.

#### Specific features:

- \* The trapezium articulates with the metacarpal bone of the thumb.
- \* The largest of the carpal bones, the capitate, articulates with the base of the metacarpal III.
- \* The Hamate, which is positioned just lateral and distal to the pisiform, has a prominent hook (Hook of Hamate) on its palmar surface that projects anteriorly
- \* Dislocation of lunate may cause carpal tunnel syndrome. In the wrist, the most commonly

dislocated carpal bone is lunate. Lunate dislocation can be caused by a fall on an outstretched hand or hyperextensions of the wrist. This mechanism displaces the lunate in a volar direction. Volar displacement some time compresses the median nerve.





**Upper Limb** 

#### Chapter 1

#### Joints of Upper Limb

#### Condyloid or ellipsoids joint

- Wrist joint-----synovial Ellipsoid joint
- CMC and Metacarpophalangeal joints
- Atlanto-occipital joint

#### Hinge joint

- · Knee
- Elbow
- · Ankle
- Interphalangeal joint

#### Saddle joint:

- Ist Carpo-metacarpal joint of the thumb, between metacarpal 1 and the trapezium Pronation and supination:
- Pronation and supination of the hand occur entirely in the forearm
- Occur on Proximal radio-ulnar joint (Synovial Pivot joint)
- The biceps brachii muscle, the largest of the four muscles that supinate and pronate the hand, is a powerful supinator as well as a flexor of the elbow joint. The long head of the biceps brachii muscle travels inside the capsule from its attachment to the supraglenoid tubercle of the scapula.
- Pronation results from the action of the pronator teres and pronator quadratus muscles

#### J ....

#### **Anatomical Snuffbox**



- The anatomical snuffbox (also known as the radial fossa), is a triangular depression found on the lateral aspect of the dorsum of the hand. It is located at the level of the carpal bones, and best seen when the thumb is extended.
- In the past, this depression was used to hold snuff (ground tobacco) before inhaling via the nose hence it was given the name 'snuffbox'.

#### Boundaries:

- Lateral border: Formed by the tendons of the abductor pollicis longus and extensor pollicis brevis;
- Medial border: Formed by the tendon of the extensor pollicis longus;
- Floor: Formed by the scaphoid and trapezium, and distal ends of the tendons of the
  extensor carpi radialis longus and extensor carpi radialis brevis.

#### Content:

- Radial artery and radial nerve
- Cephalic vein.
- Scaphoid bone (form the floor of the snuff box)

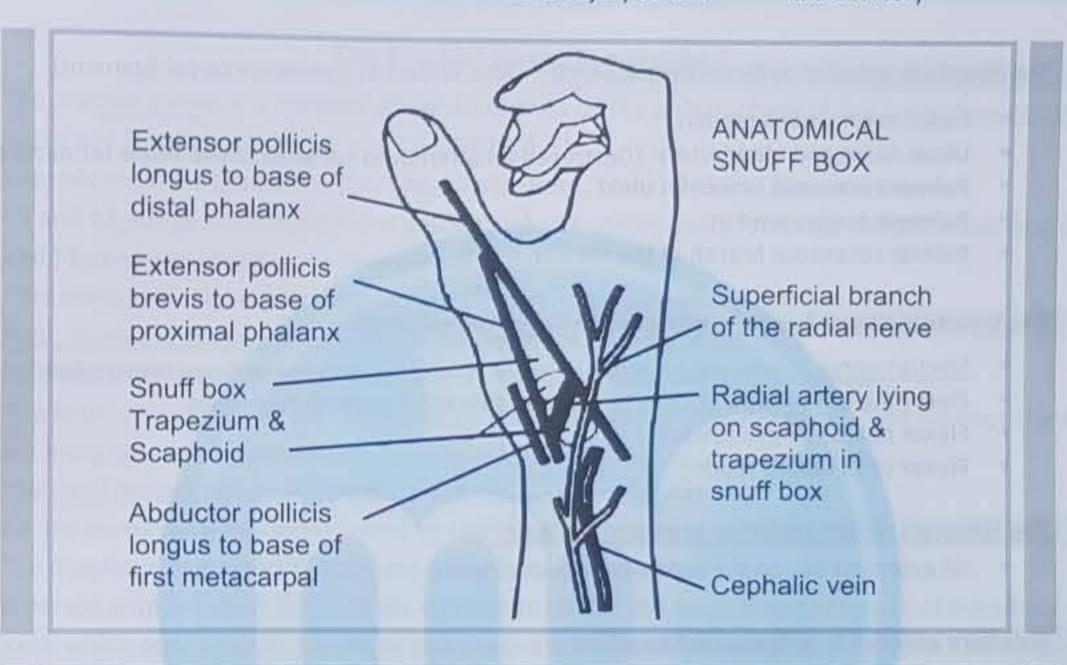
#### Clinical importance:

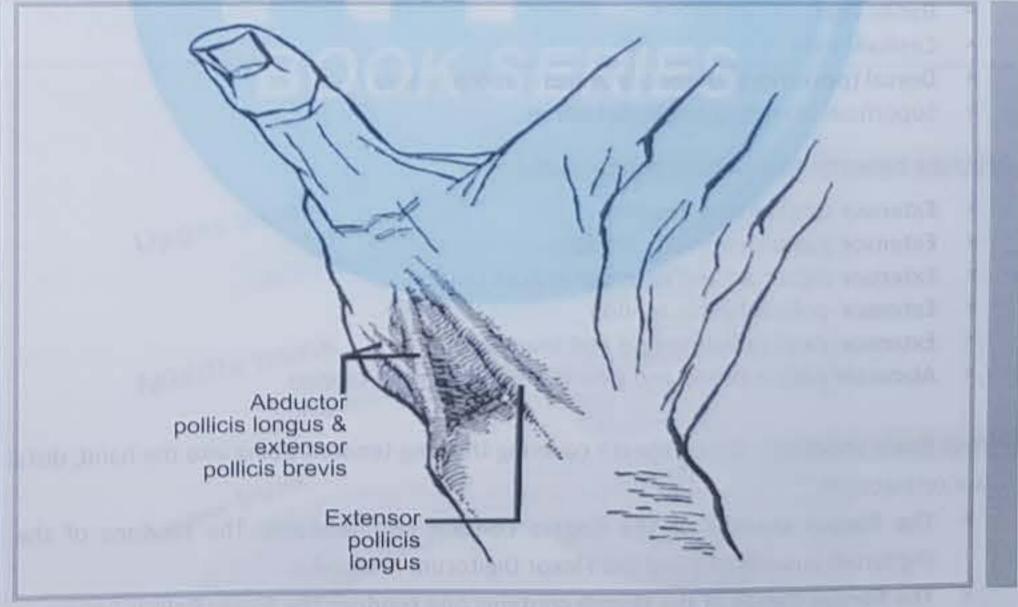
The anatomical snuffbox is an important clinical region.

#### Chapter 1

Upper Limb

- When the hand is in ulnar deviation, the scaphoid becomes palpable within the snuffbox.
- This position enables the physician to palpate the bone to assess for a fracture.
- The pulse of the radial artery can also be felt in the snuffbox.
- Bleeding from anatomical snuff box due to injury to the ----- Radial artery





Wrist



Chapter 1

#### The Structure on the anterior aspect of the wrist:

All flexors are on the anterior aspect of the wrist

#### The Structure anterior to flexor retinaculum: (Also known as transverse carpal ligament)

- · Flexor carpi ulnaris tendon
- Ulnar nerve and ulnar artery (Destroyed on attempt to cut wrist above flexor retinaculum).
- Palmar cutaneous branch of ulnar
- Palmaris longus tendon
- Palmar cutaneous branch of the median nerve

#### The Structure passes beneath/posterior to flexor retinaculum:

- Median nerve (Destroyed on attempt to cut wrist deep and below flexor retinaculum).
- Flexor digitorum superficialias tendons and Flexor digitorum Profundus
- Flexor pollicis longus tendon
- Flexor carpi radials tendon

#### The Structure on the posterior aspect of the wrist

All extensors are on the posterior aspect of wrist

#### Structure anterior to extensor retinaculum:

- Basilic vein
- Cephalic vein
- Dorsal (posterior) cutaneous branch of ulnar nerve
- Superficial branch of the radial nerve

#### Structure beneath to extensor retinaculum:

- Extensor carpi ulnaris tendon
- Extensor digitorum minimi tendon
- Extensor digitorum and extensor indices tendon
- Extensor pollicis longus tendon
- Extensor carpi radials longus and brevis tendon
- Abductor pollicis brevis and extensor pollicis brevis tendon

Fibrous flexor sheaths: Strong sheath covering the long tendons going into the hand, distal to the flexor retinaculum.

- The fibrous sheaths of the fingers contain two tendons: The tendons of the Flexor Digitorum Superficialis and the Flexor Digitorum Profundus.
- The fibrous sheath of the thumb contains one tendon: The Flexor Pollicis Longus.

Nerve Supplies of Upper Limb

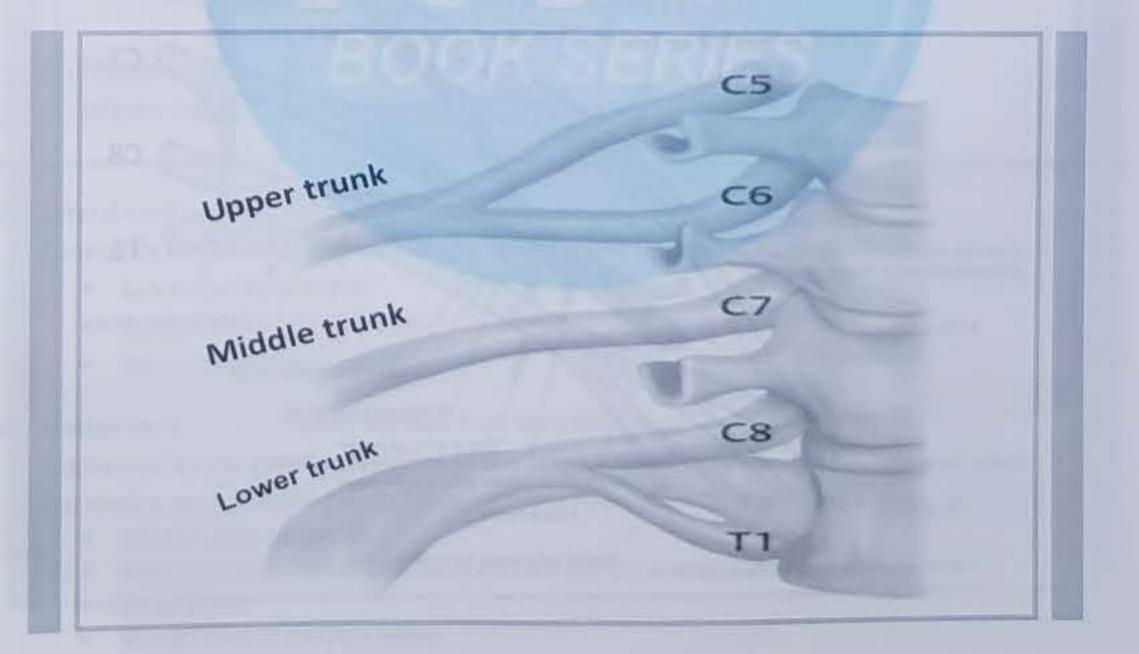
#### **Brachial Plexus**

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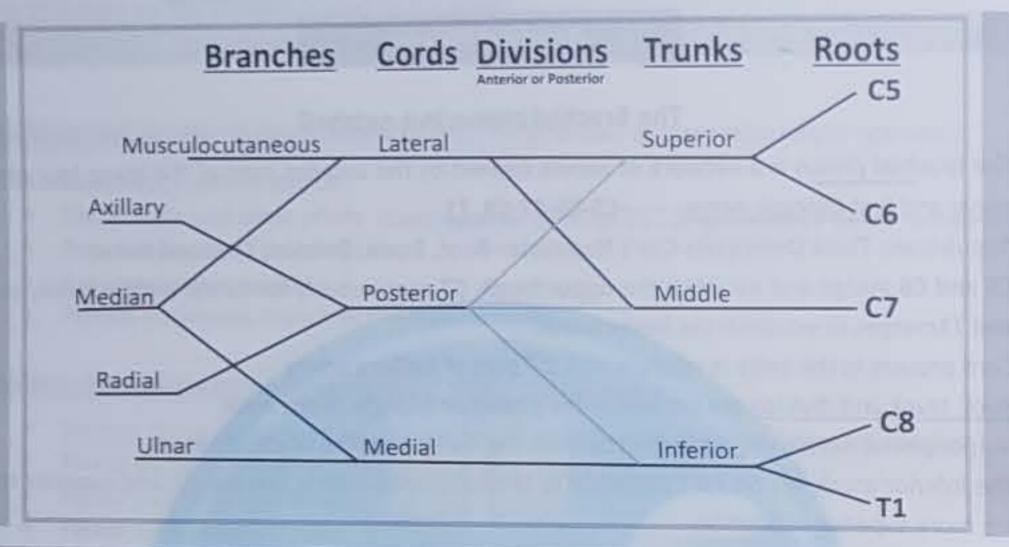
**Upper Limb** 

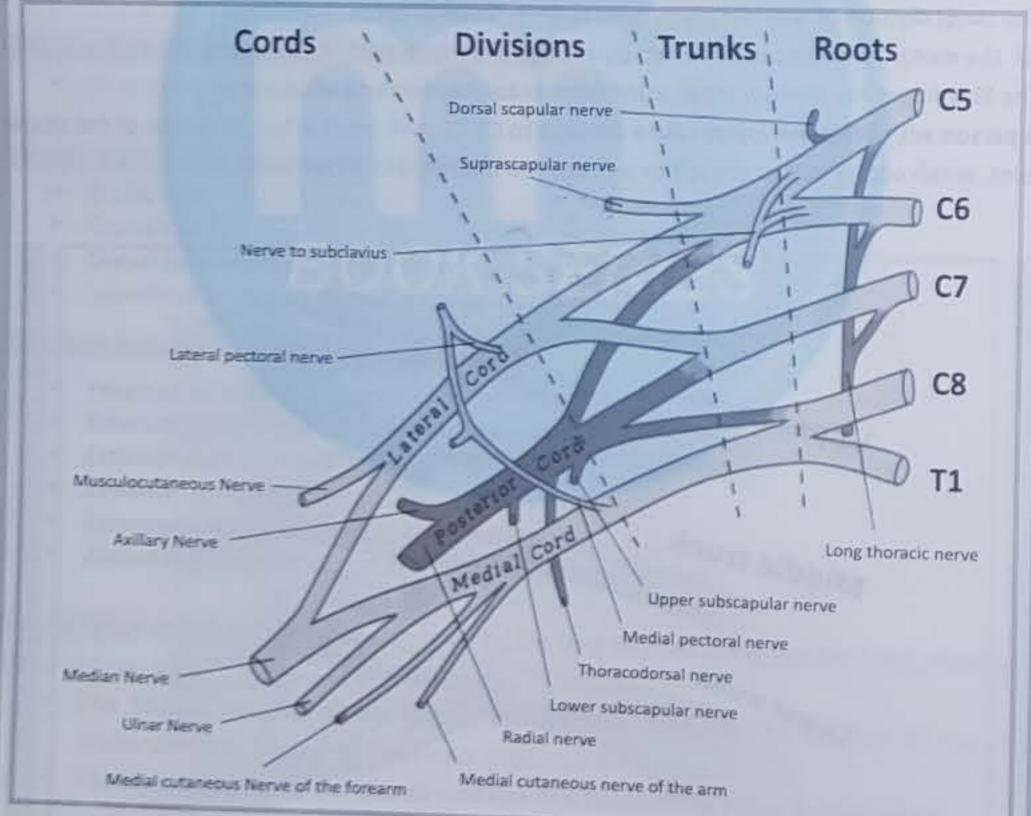
#### The Brachial plexus in a nutshell

- Republicans Think Democrats Can't Negotiate--Root, Trunk, Division, Cord and Nerve
- C5 and C6 merge and establish the upper trunk; C7 continuously forms the middle trunk, and C8 and T1merges to establish the lower trunk.
- Cord present in the axilla in relation with 2<sup>nd</sup> part of Axillary artery
- Root, trunk and division are present in the posterior triangle of the neck
- No peripheral nerves originate directly from the divisions of the brachial plexus.
- The inferior trunk lies on rib I posterior to the subclavian artery; the middle and superior trunks
  are more superior in position.
- The six(6) division of brachial plexus unit to form three(3) cords
- All the motor function can be tested by eliciting the movement of the thumb
- The Ring finger has sensory innervation from radial, median and ulnar nerve
- A person with Whiplash injury cause damage to C5-C6 will result in loss of flexion of the elbow joint, which occurs due to any jolt or jerk beyond the range of movement



The best way to memorise the brachial plexus is by drawing it -I would suggest you getting some paper and drawing out the plexus yourself as well to help it stick in your mind. Enjoy!





The brachial plexus is easier to learn if you break it down into its component segments and tackle them at a time: these are roots, trunks, division, cords and terminal branches

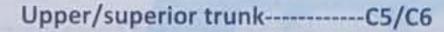
#### Root

1) Dorsal scapular nerve: C5

Chapter 1

- Supplies Levator scapulae (elevates scapula), rhomboid major and rhomboid minor
- This nerve doesn't cross the axilla
- No sensory supply
- 2) Long thoracic nerve: C5/C6/C7
  - Supplies Serratus anterior (protracts and stabilizes scapula)
  - No sensory supply
  - Clinical significance: The long thoracic nerve often crops up in exam questions. An injury to the long thoracic nerve, for example as a result of a sports injury or damage during axillary surgery, results in "winging" of the scapula.

#### Trunks



- Nerve to subclavius
  - ✓ Supply subclavius muscle (depresses clavicle and elevates the first rib)
  - ✓ No sensory supply
- <u>Suprascapular nerve</u>: ISS
  - ✓ Supplies Supraspinatus and Infraspinatus muscle
  - ✓ Sensory supply: Glenohumeral and acromioclavicular joints
- Middle trunk: formed by the root C7
  - Inferior trunk: formed by the root of C8 and T1

#### Cords

1) Lateral cord-----Lucky Loves Me------Root value (C5-C7)

Formed by the anterior divisions of the superior and middle trunk of the brachial plexus

- Lateral pectoral nerve
- Lateral root of median nerve
- Musculocutaneous nerve
- 2) Medial cord: -----Most Medical Men Uses Morphine

It is formed by the anterior divisions of the inferior trunk only

The medial cord of the brachial plexus, carrying fibers from C8 and TI and has five branches

- Medial pectoral nerve
- Medial cutaneous nerve of arm and Medial cutaneous nerve forearm
- Ulnar nerve
- Medial root of median nerve

3) Posterior Cord: ------ULTRA------Root value (C5-T1)

It is formed by the posterior division of the superior, middle and inferior trunks

- Upper subscapular
- Lower subscapular nerve
- Thoracodorsal nerve
- Radial nerve (Supply all the Extensor Muscles of the Arm and forearm).
- · Axillary nerve

#### **Axillary Nerve**

#### Supplies:

- Motor supply
  - √ Teres minor
  - ✓ Deltoid
- · Sensory supply
  - ✓ The Skin over the lower half of deltoid. "Sergeant's patch" over the lower deltoid.

#### Nerve injury sites:

- Anterior dislocation of shoulder joint cause injury to the Axillary nerve
- Sub glenoid displacement of the head of the humour into quadrangular space cause injury to the axillary nerve
- Surgical neck fracture cause injury to:
  - ✓ Nerve——Axillary nerve
  - ✓ Artery——Posterior circumflex artery

#### Musculocutaneous Nerve

- \* The Musculocutaneous nerve leaves the axilla and enters the arm by passing through the coracobrachialis muscle
- Motor innervation to all muscles in the anterior/flexor compartment of the arm
- Sensory innervation to the skin on the <u>lateral surface of the forearm</u>, that's why the lateral <u>surface of forearm sensation is spared in axillary block</u>
- Motor innervation: BBC

  - ✓ Brachialis---
  - ✓ Coracobrachialis ——Weak adductor

Axillary nerve	ibution of Main Nerves (Motor supply)  Deltoid and Teres minor	
Musculocutaneous nerve Muscle of anterior compartment of arm (flexor)		
Median Nerve	Most of the flexor muscles of forearm and LOAF muscles of hand	
Ulnar nerve	FCU and part of FDP (forearm) and all intrinsic muscles of hand except LOAF Muscles	
Radial nerve	Innervates all extensor muscle of arm and forearm	

#### Ulnar Nerve (C8-T1)



- This is the larger of the two terminal branches of the medial cord of the brachial plexus
- It passes posterior to the medial epicondyle of the humerus and then into the anterior compartment of the forearm.
- Posterior to medial epicondyle------where the ulnar nerve is referred to in lay terms as the "crazy/funny bone" -----it is superficial, easily palpable and vulnerable to injury
- It is also called Musician nerve

Chapter 1

The medial collateral ligament of the elbow joint is closely related to the Ulnar nerve Arm: The ulnar nerve has no major branches in the arm.

Forearm: In the forearm, the ulnar nerve innervates

- Muscular branches to the flexor carpi ulnaris and to the medial half of the flexor digitorum profundus arise soon after the ulnar nerve enters the forearm
- ✓ Two small cutaneous branches:
  - The palmar branch originates in the middle of the forearm and passes into the hand to supply skin on the medial side of the palm
  - o The larger dorsal branch originates from the ulnar nerve in the distal forearm and passes posteriorly deep to the tendon of the flexor carpi ulnaris and <u>innervates skin</u> on the dorsomedial side of the back of the hand and most skin on the posterior surfaces of the medial one and one-half digits.

#### Hand:

- The ulnar nerve enters the hand lateral to the pisiform and dorsomedially to the ulnar artery. Immediately distal to the pisiform, it divides into a deep branch, which is mainly motor and a superficial branch, which is mainly sensory.
  - The deep branch of the ulnar nerve passes with the deep branch of the ulnar artery. It penetrates and supplies the hypothenar muscles to reach the deep aspect of the palm, arches laterally across the palm, deep to the long flexors of the digits, and supplies the interossei, adductor pollicis, and the two medial lumbricals
  - The superficial branch of the ulnar nerve innervates the palmaris brevis muscle and continues across the palm to supply skin on the <u>palmar surface of the little finger and</u> the medial half of the ring finger

Sensory supply	HILA Muscle	
✓ Hypothenar eminence	✓ Hypothenar eminence	
✓ Medial ⅓ of the palm of the hand	✓ Interossei	
✓ Palmar aspect of the medial 1½ fingers	✓ Medial two Lumbricals	
✓ Medial ⅓ of the dorsum of the hand	✓ Adductor pollicis	
✓ Dorsal aspect of the medial 1½ fingers		

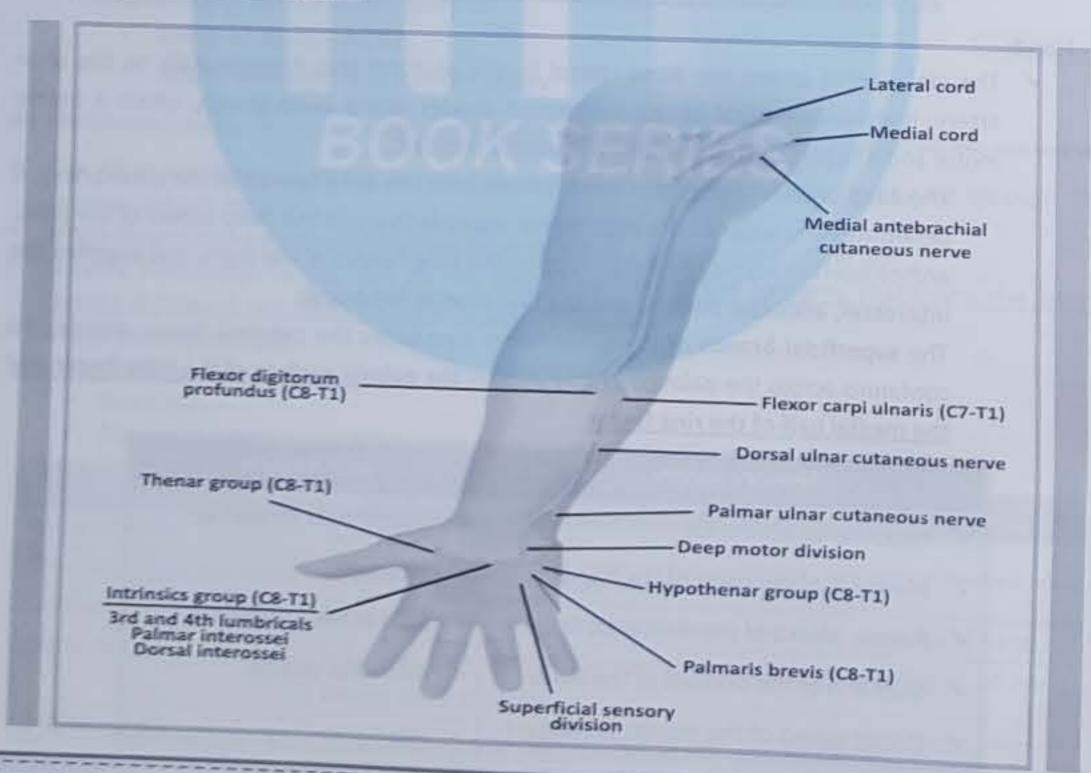
#### Chapter 1

#### Ulnar nerve injury:

- ✓ Ulnar nerve injury commonly occurs where the nerve passes posterior to the medial epicondyle of the humerus
- ✓ At the wrist, the ulnar nerve passes superficial to the flexor retinaculum and lies <u>lateral to</u> the pisiform bone.

#### Injury characterized by

- ✓ Claw hand—Which the metacarpophalangeal joints of the fingers are hyperextended and the interphalangeal joints are flexed because the function of most of the intrinsic muscles of the hand is lost. Clawing is most pronounced in the medial fingers because the function of all intrinsic muscles of these digits is lost while in the lateral two digits
- ✓ Total claw: is caused by loss of lumbricals
- ✓ Cubital tunnel syndrome: the ulnar nerve may be compressed in the cubital tunnel formed
  by the tendinous arch joining the humeral and ulnar head of attachment of the flexor carpi
  ulnaris
- ✓ Guyon's canal syndrome: Compression of the ulnar nerve may occur at the wrist where it passes between the Pisiform and hook of the hamate. The depression between these bones is converted by the piso-hamate ligament into osseofibrous tunnel (Guyon's canal). The compression of the ulnar nerve in this tunnel may result in hypoesthesia in the medial one and a half digits and weakness of the intrinsic muscle of the hand
- After ulnar nerve injury, patients are likely to have <u>difficulty making a fist</u> because of the loss of paralysis of most intrinsic hand muscles. There will be an altered sensation of <a href="https://www.hypothenareminence">hypothenareminence</a>



#### Median Nerve (C6-T1)



**Upper Limb** 

- The median nerve arises by two roots, one from the lateral cord of the brachial plexus (C6 and C7 fibers) and one from the medial cord (C8 and T1 fibers)
- The median nerve is formed anterior to the third part of the axillary artery by the union of lateral and medial roots originating from the lateral and medial cords of the brachial plexus
- Medial nerve injury is the most disabling injury because it is the labourer's nerve
- The Median nerve is the "eye of hand"
- The sensory innervation of the nail bed of the index finger is the median nerve.

#### Branches:

- The largest branch of the median nerve in the forearm is the anterior interosseous nerve, which originates between the two heads of pronator teres, passes distally down the forearm with the anterior interosseous artery, innervates the muscles in the deep layer (flexor pollicis longus, the lateral half of flexor digitorum profundus, and pronator quadratus) and terminates as articular branches to joints of the distal forearm and wrist
- A small palmar branch originates from the median nerve in the distal forearm immediately proximal to the flexor retinaculum, passes superficially into the hand and innervates the skin over the base and central palm. This palmar branch is spared in carpal tunnel syndrome because it passes into the hand superficial to the flexor retinaculum of the wrist.

#### Sensory supply

- ✓ Thenar eminence, the lateral ¾ of the palm of the hand
- ✓ Palmar aspect of lateral 3½ fingers
- ✓ Dorsal fingertips of lateral 3½ fingers

#### Muscle supplies:

- ✓ Arm: The median nerve has no major branches in the arm
- ✓ Forearm: Supplies muscles in the anterior compartment of the forearm (except for the flexor carpi ulnaris muscle and the medial half of the flexor digitorum profundus muscle, which are innervated by the ulnar nerve).

#### Hand: Supply in hand: LOAF

- ✓ L-----Lateral two lumbricals
- ✓ O-----Opponens pollicis---Cause opposition of thumb with the little finger
- ✓ A-----Abductor pollicis brevis
- ✓ F----Flexor pollicis brevis
- ✓ Explanation:
  - Three thenar muscles---OAF
  - The skin over the palmar surface of the lateral three and one-half digits and over the lateral side of the palm and middle of the wrist.

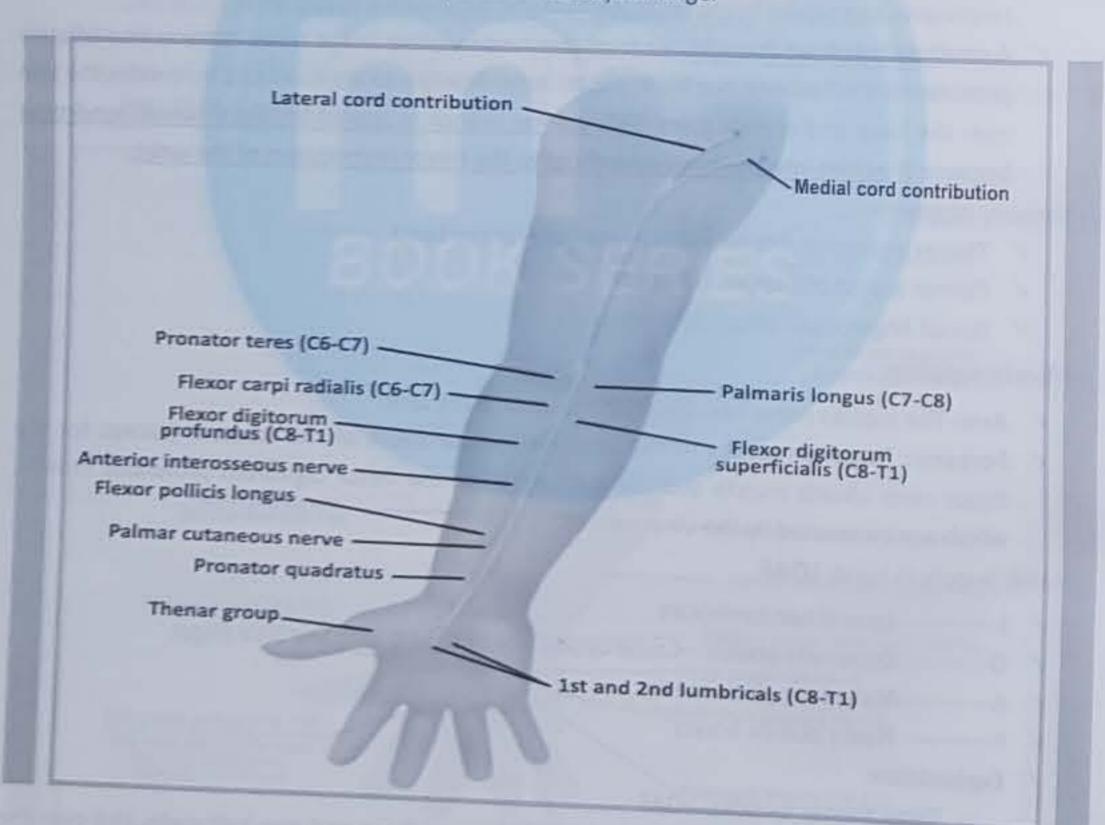
The ability to grasp an object between the pad of the thumb and the pad of one of the fingers depends on the normal functioning of the thenar muscles, which are innervated by the recurrent branch of the median nerve carrying fibers from the spinal cord level C8 (T1).

#### Injury occurring sites:

- ✓ Supracondylar fracture
- ✓ Dislocation of lunate—a carpal bone
- ✓ Injection in the cubital fossa

#### Injury cause:

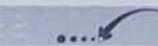
- Carpal tunnel syndrome: The main feature is wastage of thenar muscle without loss of sensation on this area
- ✓ Pointing index
- ✓ Ape thumb
- ✓ Loss of abduction of thumb without loss of adduction
- ✓ You will be unable to hold bell-point or count your finger



Chapter 1

#### Upper Limb

#### Radial Nerve (C5-C8)



- The radial nerve is the largest terminal branch of the posterior cord
- Supply All muscles in the posterior compartments of the arm and forearm, which are Extensor muscles
- The skin on the posterior aspect of the arm and forearm, the lower lateral surface of the arm, and the dorsal lateral surface of the hand.
- It is accompanied through the triangular interval by the Profunda brachii artery
- The radial nerve enters the forearm anterior to the lateral epicondyle of the humerus, just deep to the Brachioradialis muscle.
- In the lateral wall of the cubital fossa, and <u>before dividing</u> into superficial and deep branches, the <u>radial nerve innervates the Brachioradialis and extensor carpi radialis longus muscles.</u>
- The radial nerve is located near the lateral epicondyle and ulnar nerve located near the medial epicondyle

#### Branches:

The radial nerve bifurcates into deep and superficial branches under the margin of the brachioradialis muscle in the lateral border of the cubital fossa

- ✓ The deep branch is predominantly motor and passes between the two heads of the supinator muscle to access and supply muscles in the posterior compartment of the forearm.
- ✓ The superficial branch of the radial nerve is sensory. It passes down the anterolateral aspect of the forearm deep to the brachioradialis muscle and in association with the radial artery. Approximately two-thirds of the way down the forearm, the superficial branch of the radial nerve passes laterally and dorsally around the radial side of the forearm deep to the tendon of the brachioradialis. The nerve continues into the hand where it innervates skin on the dorsolateral surface.
- ✓ The superficial branch of the radial nerve innervates skin over the dorsolateral aspect of the palm and the dorsal aspects of the lateral three and one-half digits distally to approximately the terminal interphalangeal joints.
- ✓ Terminal branches of the nerve can be palpated or 'rolled' against the tendon of the extensor pollicis longus as they cross the anatomical snuffbox.
- ✓ The sensory innervation of the dorsal surface of the root of the thumb is the radial nerve

Sensory supply	Supply BEATS Muscle
✓ Posterior arm and forearm	✓ BBrachioradialis
✓ Lateral ¾ of the dorsum of the hand	✓ EExtensor
✓ Proximal dorsal aspect of lateral 3½	✓ AAnconeus
fingers	✓ TTriceps
	✓ SSupinator

#### ✓ Fracture of mid-shaft of the humerus:

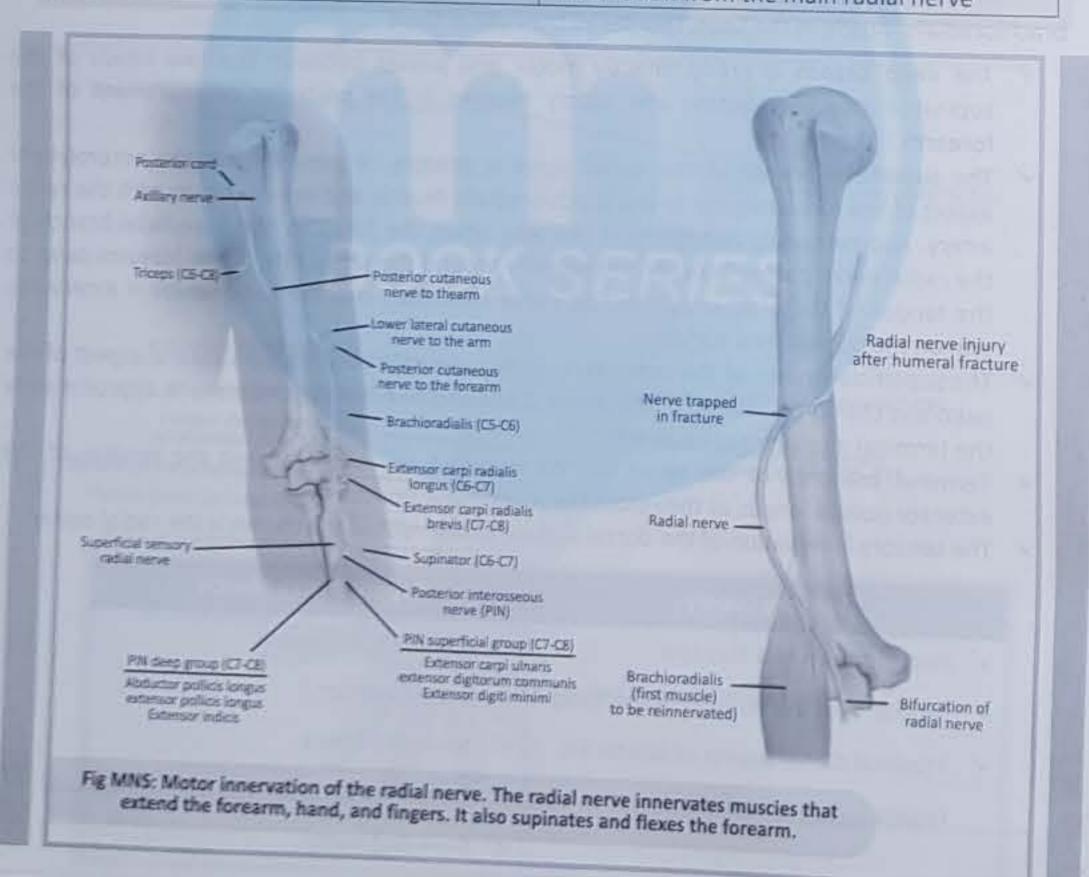
- o Injury to profunda brachia artery ,because The radial nerve is tightly bound with the profunda brachii artery between the medial and lateral heads of the triceps brachii muscle in the radial groove
- o Injury to radial nerve, remember spare the long head of triceps that's why the extension is still possible
- o In humerus fractures, nerves affected include: axillary, radial and ulnar
- ✓ Scaphoid bone fracture——Radial nerve and Radial artery

#### **Wrist Drop** The characteristic handicap is the inability to extend the wrist resulting from paralysis of the extensor muscle of the forearm.

The hand is flexed at the wrist and lies flaccid

#### Finger drop without Wrist drop

Finger drops (inability to extend finger) without wrist drop: Posterior interosseous nerve injury, which is a branch of radial nerve. Damage to posterior interosseous nerve doesn't cause wrist drop because extensor carpi radials longus receive it innervation from the main radial nerve



#### Chapter 1

Upper Limb

# Clinical and Applied Anatomy



- Site of injury: injury to upper/superior trunk C5/C6) occasionally the middle trunk (C7) is also involved
- Nerve root involves: mainly C5/C6, Causes:
  - The classical cause is a traction injury during difficult or obstructed childbirth, such as shoulder dystocia requiring emergency forceps delivery, or breech presentations with the arms raised above the head.
  - The stretching mechanism can also be caused by falls onto the neck/shoulder or excessive traction on the arm, for example during sports (often known as "burner syndrome"), motor biking accidents or attempts to reduce a shoulder dislocation.
  - ✓ undue separation of the head from shoulder joint due to birth injury, falling on shoulder. and anesthesia
- Nerve injured: Musculocutaneous nerve, Axillary nerve, Suprascapular nerve and Nerve to subclavius
- Clinical features:
  - ✓ Erb's palsy results in loss of sensation to the skin over the "sergeant's patch", lateral arm. and lateral forearm.
  - ✓ There is wasting of the deltoid, supraspinatus and infraspinatus muscles and the anterior. compartment of the arm, with loss of shoulder abduction and external rotation, elbow flexion and wrist supination. This results in a "waiter's tip" deformity characterized by a limp, adducted, internally rotated shoulder, an extended elbow and a pronated wrist. Biceps reflex is absent.
  - ✓ Cause loss of ALFS: Abduction, Lateral rotation, Flexion and Supination

#### Klumpke's Palsy

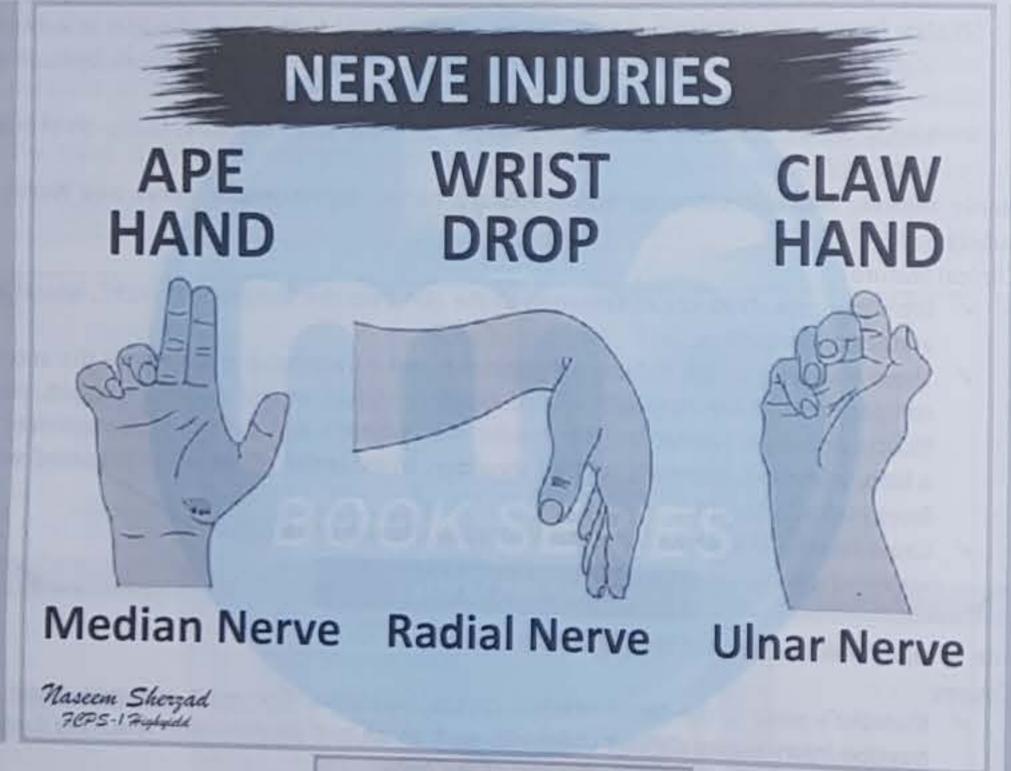


- Site of injury: Inferior trunk of brachial plexus---C8-T1
  - Causes:
    - √ Klumpke's palsy is the rarest brachial plexus syndrome. The most common cause is a traction injury during difficult childbirth, such as an arm presentation requiring force on the arm to successfully deliver the rest of the baby.
    - √ The same mechanism can also be caused by a falling person grabbing onto something (e.g. grabbing a branch when falling from a tree), or by other causes of excessive abduction such as motor biking accidents.
    - ✓ It can also be caused by compression of the lower plexus by a mass in the root of the neck, such as lymphoma or lung cancer.
    - ✓ A cervical rib or supernumerary rib can compress T1, subclavian artery and lower trunk resulting in thoracic outlet syndrome
- Nerve injured: median and Ulnar
- A person with Whiplash injury cause damage to C5-C6, will result in loss of flexion of elbow joint

#### Surgical Neck of Humerus



- One of the most important features of the proximal end of the humerus is the surgical neck.
- This region is oriented in the horizontal plane between the expanded proximal part of the humerus (head, anatomical neck, and tubercles) and the narrower shaft.
- The Axillary nerve and the posterior circumflex humeral artery, which pass into the deltoid region from the axilla, do so immediately posterior to the surgical neck.
- Because the surgical neck is weaker than more proximal regions of the bone, it is one of the sites where the humerus commonly fractures.
- The associated nerve (Axillary) and artery (posterior circumflex humeral) can be damaged by fractures in this region.



#### DR-CUMA

Drop-----Radial Nerve Claw-----Ulnar nerve Median ---- Ape hand

# **Summary of Brachial Plexus**

I hope you found this portion of anatomy helpful and now feel able to approach this nightmarish subject with confidence. Once you have triumphed over the brachial plexus, you have officially won Chapter 1

**Upper Limb** 

# Arterial System, Venous System And Lymphatic Drainage Of Upper Limb

#### Arterial System



#### **Axillary artery**

- Begins at the lateral part of the first rib as a continuation of the subclavian artery and
- Ends at the lower border of teres major muscle and continue as the brachial artery
- During its course via axilla, it is crossed on its superficial aspect by the pectoralis minor muscle, which divides it into 3 parts. The axillary vein is medial to the artery and the cords of brachial plexus are arranged around the 2nd part of the artery (i.e. part deep to the pectoralis minor); the lateral cord being lateral, the medial cord medial, and posterior cord behind.
- Throughout its course, the artery is closely related to the cords of the brachial plexus and their branches and is enclosed with them in a connective tissue sheath called the axillary sheath. If this sheath is traced upward into the root of the neck, it is seen to be continuous with the prevertebral fascia.
- The axillary artery comprises of 6 branches: 1 branch from the first part, 2 branches from the next part, and 3 branches from the third part. The Majority of these branches go towards the walls of the axilla.

#### Ist part:----One branch

- Superior (or proximal) to the Pectoralis minor muscle
- Branch:
  - ✓ Superior or highest thoracic artery

#### 2<sup>nd</sup> part----Two branches

- Posterior (or deep) to the Pectoralis minor muscle
- Branches:
  - ✓ Thoracoacromial artery: pierces clavipectoral fascia and soon breaks up into 4. branches
  - ✓ Lateral thoracic artery: In the females, the lateral thoracic artery is large and gives significant supply to the breast via its lateral mammary branches.
- Relations:
  - ✓ Anteriorly:----- Pectoralis minor and pectoralis major
  - Posteriorly: -----Posterior cord of the brachial plexus
  - Laterally: -----Lateral cord of the brachial plexus
  - Medially:-----Medial cord of the brachial plexus and axillary vein

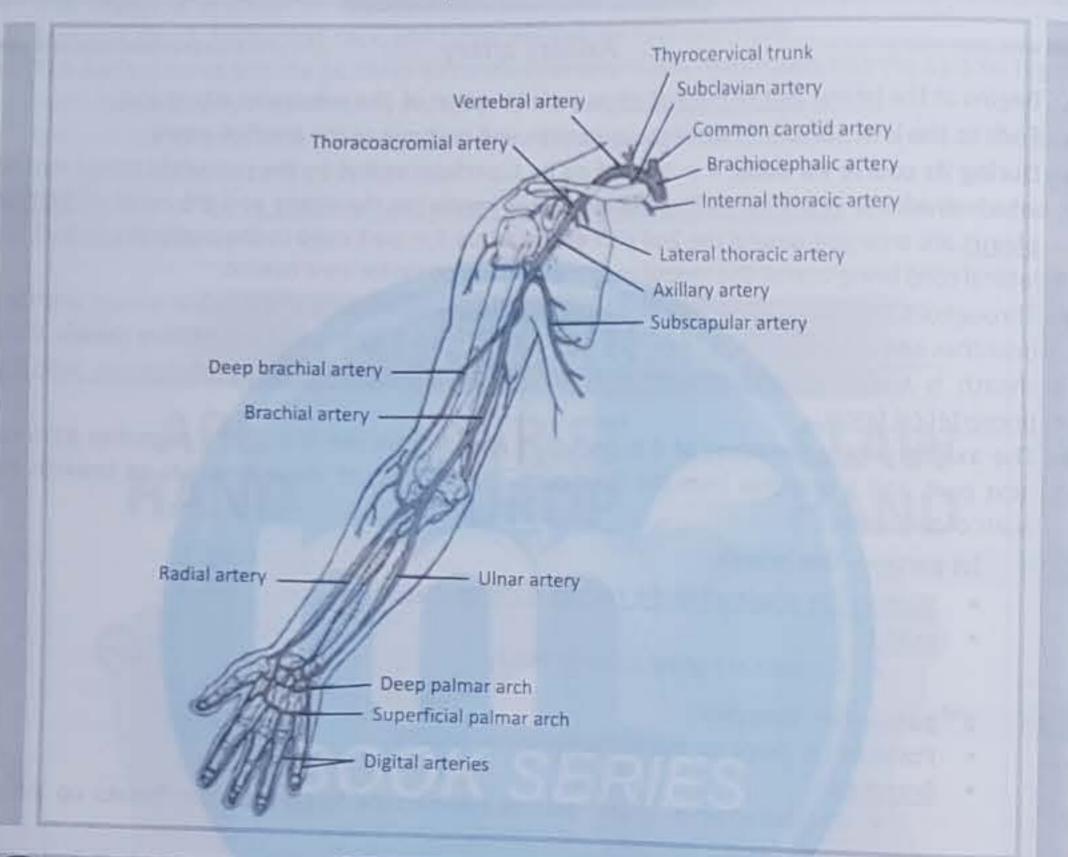
#### 3rd part---3 branches

- Inferior (or distal) to the Pectoralis minor muscle
- Branches:
  - ✓ Subscapular artery----largest branch
  - ✓ Anterior circumflex Humeral artery
  - ✓ Posterior circumflex Humeral artery

#### Blood supply of humorous humerus:

- · Head:
  - ✓ Arcuate artery-----First click this, if not in option then

- ✓ Anterior circumflex artery
- " Neck:
  - ✓ Anterior circumflex artery
  - ✓ Posterior circumflex artery



- **Brachial Artery**
- The brachial artery, is found in the anterior compartment and not a content of axilla
- . Beginning as a continuation of the axillary artery at the lower border of the teres major muscle . Course: The artery at first is located on the medial side of the arm, then the artery gradually comes forwards in front of the elbow joint between the 2 epicondyles of the <u>humerus</u>. The course of the median nerve relative to brachial artery in the upper arm, Lateral to anterior to medial
- . End: It terminates just distal to the elbow joint where it divides into the radial and ulnar arteries.
  - Profunda brachii artery (largest and first branch):
    - The profunda brachii artery, the largest branch of the brachial artery, passes into and supplies the posterior compartment of the arm
    - o It accompanies the radial nerve with which it immediately leaves the lower triangular intermuscular space to goes into the spiral groove on the posterior surface of the humerus.
  - Nutrient artery to humerus enters the nutrient foramen of humerus located near the

insertion of coracobrachialis.

- Superior ulnar collateral artery originates near the middle of the arm and accompanies the ulnar nerve.
- Inferior ulnar collateral (or supratrochlear artery) originates near the lower end of humerus and divides into the anterior and posterior branches, which take part in the formation of arterial Anastomosis around the elbow.
- Radial and ulnar arteries (terminal branches)

#### Clinical significance:

- Brachial pulse: The brachial pulse is commonly felt in the cubital fossa medial to the tendon of biceps and its pulsations are auscultated for recording the blood pressure. The biceps tendon is easily palpable on flexing the elbow.
- Compression of brachial artery: The brachial artery can be effectively compressed against the shaft of humerus in the level of insertion of coracobrachialis to stop the hemorrhages in the upper limb occurring from any artery distal to the brachial artery, example, bleeding wounds of the palmar arterial arches.
- Rupture of the brachial artery in supracondylar fracture of the humerus may result in Volkmann's ischemic contracture.

Chapter 1

#### Radial Artery



Upper Limb

- The radial artery originates from the brachial artery at approximately the neck of the radius and passes along the lateral aspect of the forearm
- In the distal forearm, the radial artery can be located using the flexor carpi radialis muscle as a landmark. The radial pulse can be felt by gently palpating the radial artery against the underlying muscle and bone.
- The radial artery contributes substantially to the supply of the thumb and the lateral side of the index finger;
- The remaining digits and the medial side of the index finger are supplied mainly by the ulnar artery
- It passes between the two heads of the first dorsal interosseous muscle and then between the two heads of the adductor pollicis to access the deep plane of the palm and form the deep palmar arch.
- . Clinical notes: In the distal part of the radius the radial artery lies on the anterior surface of the radius and is coverd only skin and fascia. Here, the artery has the tendon of brachioradials on its lateral side and tendon of flexor carpia radials on its medial side (site for taking radial pulse)



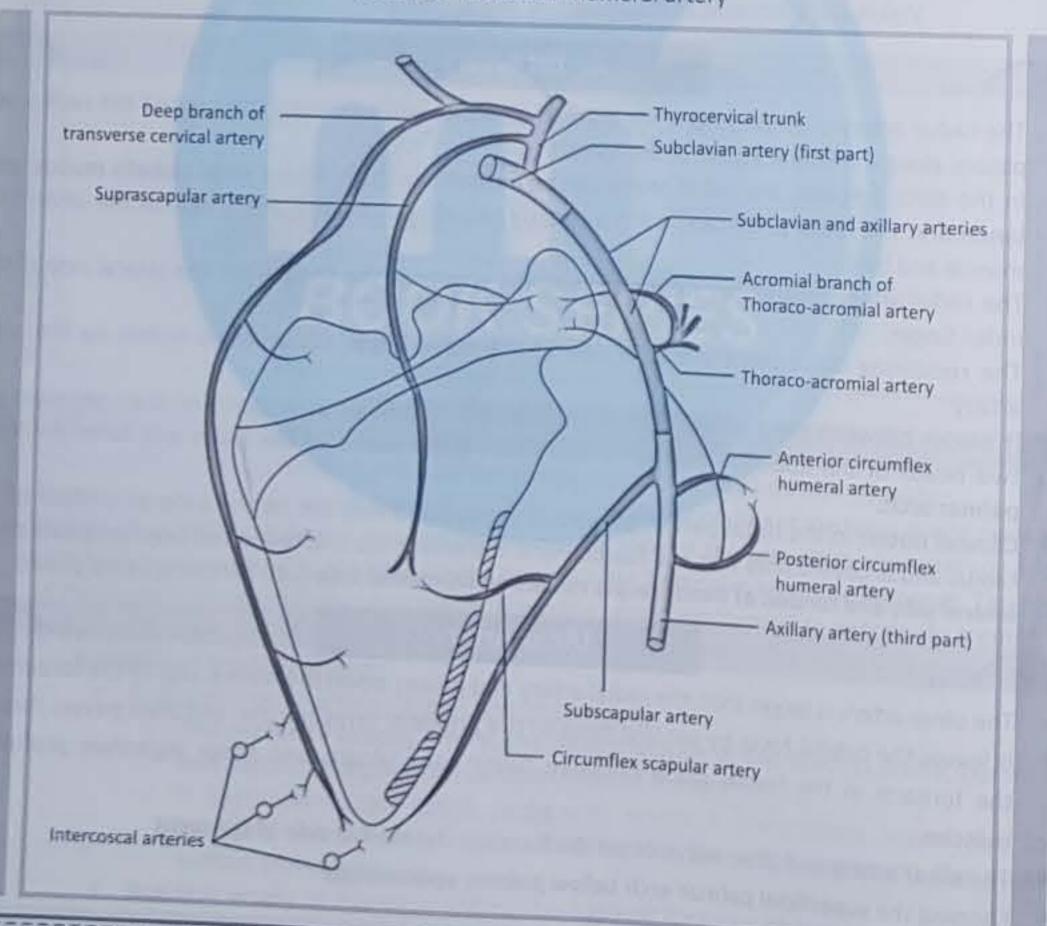
#### **Ulnar Artery**



- The ulnar artery is larger than the radial artery and passes down the medial side of the forearm.
- It leaves the cubital fossa by passing deep to the pronator teres muscle, and then passes through the forearm in the fascial plane between flexor carpi ulnaris and flexor digitorum profundus muscles.
- The ulnar artery and ulnar nerve enter the hand on the medial side of the wrist
- Forming the superficial palmar arch below palmer aponeurosis



- \* The Arterial Anastomosis around Scapula is principally created between the branches of the first part of the subclavian and the third part of the axillary arteries.
- The scapular anastomosis happens at 2 sites: around the body of the scapula and over the acromion process of the scapula.
- 1) Around the body of the scapula: It takes place between the:
  - Suprascapular artery, a branch of the thyrocervical trunk from the first part of the subclavian artery
  - Circumflex scapular artery, a branch of the subscapular artery from the third part of the axillary artery
  - Dorsal scapular artery: It most frequently arises from the subclavian artery (the second or third part), but a quarter of the time it arises from the transverse cervical artery which originates from the thyrocervical trunk.
- 2) Over the acromion process: It takes place between the:
  - Acromial branch of the thoraco-acromial artery
  - Acromial branch of the suprascapular artery
  - Acromial branch of the posterior circumflex humeral artery



Chapter 1

Upper Limb

NASEEM SHERZAD FCPS -1 HIGH-YIELD

#### 1) Basilic vein

- Arise from the medial side of the dorsal venous arch
- Ascend on the ulnar side of the forearm to the elbow
- Form Axillary vein by Basilic vein and vena comitantes of brachial artery at the lower border of teres major muscle

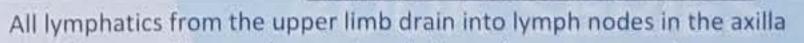
#### 2) Cephalic vein

- Arise from the lateral side of the dorsal venous arch, begins in an anatomic snuff box
- Ascend on the radial side of the forearm to elbow
- Lies in the roof of the cubital fossa
- This continuous up in arm in deltopectoral groove (a groove between the deltoid muscle and pectoralis major muscle)
- Pierce deltopectoral fascia and drain into Axillary vein in clavipectoral triangle (also known as the deltopectoral triangle)
- The vein that most likely to bleed if a sharp cut occurs at anatomical snuff box is cephalic vein
- The cephalic vein is favored vessels for arteriovenous fistula formation and should be preserved in a patient with end-stage renal failure

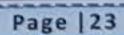
#### 3) Median cubital vein

- Link cephalic and Basilic vein in the cubital fossa
- It is a frequent site for venesection

#### Lymphatic Drainage of Upper Limb



- In addition, axillary nodes receive drainage from an extensive area on the adjacent trunk, which includes regions of the upper back and shoulder, the lower neck, the chest, and the upper anterolateral abdominal wall. Axillary nodes also receive drainage from approximately 75% of the mammary gland.
- The 20-30 axillary nodes are generally divided into groups on the basis of location:-----APICAL
  - 1) Humeral (Lateral) nodes Posteromedial to the Axillary vein receive most of the lymphatic drainage from the upper limb.
    - Supratrochlear lymph node:
      - Placed above the medial epicondyle of humerus, medial to the Basilic vein
      - Their afferents drain the Middle, ring and little finger, the medial portion of the hand and the medial side of the forearm
      - The efferent enter the lateral axillary lymph nodes
  - 2) Pectoral (Anterior) nodes occur along the inferior margin of the pectoralis minor muscle along the course of the lateral thoracic vessels and receive drainage from the abdominal wall, the chest, and the mammary gland.

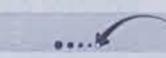


- 3) Subscapular (Posterior) nodes on the posterior Axillary wall in association with the subscapular vessels drain the posterior Axillary wall and receive lymphatics from the back, the shoulder, and the neck.
- 4) Central nodes: are embedded in axillary fat and receive tributaries from:
  - o Humeral,
  - o Subscapular, and
  - Pectoral groups of nodes
- 5) Apical nodes are the most superior group of nodes in the axilla and drain all other groups of nodes in the region. In addition, they receive lymphatic vessels that accompany the cephalic vein as well as vessels that drain the superior region of the mammary gland.
- 6) Infraclavicular nodes: The Infraclavicular nodes (subclavicular nodes) are two or three nodes situated superiorly and posteriorly to the axillary artery, inferior to the clavicle. They receive lymph from the superficial vessels around the cephalic vein. Their efferents drain directly into the apical nodes, to which they are closely associated. They drain lymph from thumb consisting of its web and upper part of the breast.
- Efferent vessels from the apical group converge to form the subclavian trunk, which usually joins the venous system at the junction between the right subclavian vein and the right internal jugular vein in the neck. On the left, the subclavian trunk usually joins the thoracic duct in the base of the neck.

#### Clinical notes:

- ✓ Lymphatic drainage from the lateral part of the breast passes through nodes in the axilla. Significant disruption to the normal lymphatic drainage of the upper limb may occur if a mastectomy or a surgical axillary nodal clearance has been carried out for breast cancer. Furthermore, some patients have radiotherapy to the axilla to prevent the spread of metastatic disease but a side-effect of this is the destruction of the tiny lymphatics as well as the cancer cells.
- If the lymphatic drainage of the upper limb is damaged, the arm may swell and pitting edema (lymphoedema) may develop

#### Muscles of Upper Limb



**Upper Limb** 

#### **Anterior Compartment**

- The anterior compartment of the arm contains three muscles-the Coracobrachialis, Brachialis, and biceps brachii muscles -which are innervated predominantly by the Musculocutaneous nerve.
- Innervation of brachialis muscle is predominantly by the Musculocutaneous nerve. A small component of the lateral part is innervated by the radial nerve.
- The biceps brachii muscle is a powerful flexor of the forearm at the elbow joint; it is also the most powerful supinator of the forearm when the elbow joint is flexed.
- Clinical notes:

Chapter 1

A 'tap' on the tendon of biceps brachii at the elbow tests predominantly spinal cord segment C6.

#### **Posterior Compartment**

- The posterior compartment contains one muscle-the triceps brachii muscle-which is innervated by the radial nerve
- Innervation of triceps brachii is by branches of the radial nerve. A 'tap' on the tendon of triceps tests predominantly spinal cord segment C7.



#### **Anterior Compartment**

- Muscles in the anterior (flexor) compartment of the forearm occur in three layers: superficial, intermediate, and deep
- · All four muscles in the superficial layer-flexor carpi ulnaris, palmaris longus, flexor carpi radialis, and pronator teres-have a common origin from the medial epicondyle of the humerus, and, except for pronator teres, extend distally from the forearm into the hand
- The muscle in the intermediate layer of the anterior compartment of forearm is the flexor digitorum superficialis muscle
- . There are three deep muscles in the anterior compartment of the forearm: flexor digitorum profundus, flexor pollicis longus, and pronator quadratus
- All muscles in the anterior compartment of the forearm are innervated by the median nerve, except for the flexor carpi ulnaris muscle and the medial half of the flexor digitorum profundus muscle, which are innervated by the ulnar nerve.

#### Posterior compartment

- The nerve of the posterior compartment of the forearm is the radial nerve. Most of the muscles are innervated by the deep branch, which originates from the radial nerve in the lateral wall of the cubital fossa deep to the brachloradialis muscle and becomes the posterior interosseous nerve after emerging from between the two heads of the supinator muscle in the posterior compartment of the forearm.
- Muscles in the posterior compartment of the forearm occur in two layers: a superficial and a deep layer

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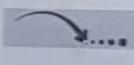
#### Upper Limb

Chapter 1

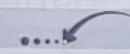
- The 5 muscles in the superficial layer are the extensor carpi radialis brevis, extensor digitorum, extensor digiti minimi, extensor carpi ulnaris, and anconeus. All have a common origin from the supraepicondylar ridge and lateral epicondyle of the humerus and, except for the brachioradialis and anconeus, extend as tendons into the hand
- The deep layer of the posterior compartment of the forearm consists of five muscles: supinator, abductor pollicis longus, extensor pollicis brevis, extensor pollicis longus, and extensor indicis
- Except for the supinator muscle, all these deep layer muscles originate from the posterior surfaces of the radius, ulna, and interosseous membrane and pass into the thumb and fingers:
- All muscles of the deep layer are innervated by the posterior interosseous nerve, the continuation of the deep branch of the radial nerve.

#### Lateral Compartment

- The two muscle of Brachioradialis and extensor carpi radialis longus,
- In the lateral wall of the cubital fossa, and before dividing into superficial and deep branches, the radial nerve innervates the Brachioradialis and extensor carpi radialis longus muscles.
- Remember: nerve supply of posterior compartment is from deep branch of radial nerve while nerve supply of lateral compartment muscle of forearm is from main trunk of radial nerve before division



#### Hand



- The intrinsic muscles of the hand are the adductor pollicis, interossei, thenar, hypothenar, Palmaris brevis, and lumbrical muscles
- The intrinsic muscles occur entirely in the hand and mainly execute precision movements ('precision grip') with the fingers and thumb.
- All of the intrinsic muscles of the hand are innervated by the deep branch of the ulnar nerve except for the three thenar and two lateral lumbrical muscles, which are innervated by the
- The intrinsic muscles are predominantly innervated by spinal cord segment T1 with a

#### Interossei

#### Dorsal interossei:

THE RESERVE THE PERSON NAMED IN COLUMN 18 YOUR PARTY.

NAME AND ADDRESS OF THE OWNER, WHEN PERSON O

- There are four bipennate dorsal interosseous muscles between, and attached to, the
- \* Function: D-Ab——The dorsal interossei are the major abductors of the index, middle, and ring fingers, at the metacarpophalangeal joints

#### Palmar interossei:

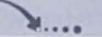
- The four palmar interossei are anterior to the dorsal interossei, and are unipennate muscles originating from the metacarpals of the digits with which each is associated
- Function: P-Ad——The palmar interossei adduct the thumb, index, ring, and little fingers with respect to a long axis through the middle finger. The movements occur at the

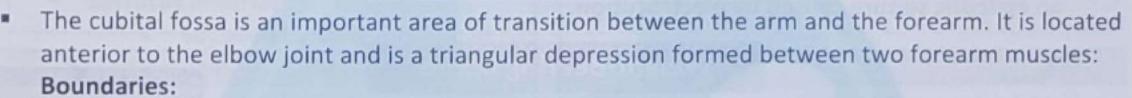
#### Chapter 1

#### **Upper Limb**

#### **Lumbrical Muscles**

- There are four lumbrical (worm-like) muscles, each of which is associated with one of the fingers. The muscles originate from the tendons of flexor digitorum profundus in the palm:
- The medial two lumbricals are innervated by the deep branch of the ulnar nerve; the lateral two lumbricals are innervated by digital branches of the median nerve
- The lumbricals are unique because they link flexor tendons with extensor tendons. Through their insertion into the extensor hoods, they participate in flexing the metacarpophalangeal joints and extending the interphalangeal joints.
  - The medial two lumbricals are bipennate and originate from the flexor digitorum profundus tendons associated with the middle and ring fingers and the ring and little fingers, respectively;
  - ✓ The lateral two lumbricals are unipennate muscles, originating from the flexor digitorum profundus tendons associated with index and middle fingers, respectively.





#### √ Base:

o The base of the triangle is an imaginary horizontal line between the medial and lateral epicondyles.

#### ✓ Medially:

o Pronator teres: The pronator teres muscle originating from the medial epicondyle of the humerus

#### √ Laterally:

Brachioradialis muscle: The Brachioradialis muscle originating from the lateral supraepicondylar ridge of the humerus

#### ✓ Roof:

- The roof of the cubital fossa is formed by superficial fascia and skin.
- O Structure in roof of cubital fossa: skin, superficial fascia, cephalic vein, Basilic vein, median cubital vein connecting the Basilic vein and cephalic vein, lateral and medial cutaneous nerves of forearm

#### √ Floor:

The bed or floor of the fossa is formed mainly by the Brachialis muscle

#### The major contents of the cubital fossa, from Median to lateral are: MBBR

- ✓ Median nerve-----most Medial structure
- Brachial artery;
- Biceps brachii muscle tendon;
- ✓ Radial nerve-----Most lateral structure

#### Clinical notes:

- ✓ When taking a blood pressure reading from a patient, the clinician places the stethoscope over the brachial artery in the cubital fossa.
- ✓ The ulnar nerve does not pass through the cubital fossa. Instead, it passes posterior to the medial epicondyle.
- ✓ Cubital Tunnel Syndrome is a condition that involves pressure or stretching of the ulnar nerve (also known as the "funny bone" nerve), which can cause numbness or tingling in the ring and small fingers, pain in the forearm, and/or weakness in the hand.

#### **Common Dislocations**

- · Hand------Most common dislocated bone-
- -Posterior dislocation Hip joint—Most common dislocation —
- -Anterior dislocation \* TMJ-----Most common dislocation --
- --- Patella Most commonly dislocated in the lower limb is---
- Most common tarsal bone dislocation-----Talus

#### **Shoulder Joint Dislocation**

- Most commonly dislocated joint in the body and most common joint to undergo recurrent dislocation. Most freely moveable joint in the body
- Most common dislocation is——Anterior dislocation, clinically all anterior dislocations are anterioinferior
- Posterior dislocation is extremely rare; when seen, the clinician should focus on its cause, the most common being extremely vigorous muscle contractions, which may be associated with an epileptic seizure caused by electrocution.

#### **Weight-Bearing Bones**

- Clavicle: Potential forces that it transmits from the upper limb to the trunk
- Coracoclavicular ligament----Transmit the weight of upper limb to axial Skelton, because it is the strongest ligament that attaching the clavicle to the rest of the pectoral girdle
- Ischial tuberosity-Weight bearing line of pelvis pass through ischial tuberosity
- Tibia (shin bone) is the larger bone and true weight-bearing bone of the leg
- Capitulum: Axis of upper limb passes through Capitulum

# Three classic injuries to the Radius and Ulna

- Monteggia's fracture is a fracture of the proximal third of the ulna and an anterior dislocation of the head of the radius at the elbow.
- Galeazzi's fracture is a fracture of the distal third of the radius associated with subluxation (partial dislocation) of the head of the ulna (distal ulna) at the wrist joint.
- Colles' fracture is a fracture, and posterior displacement, of the distal end of the radius.
- Simply remember Monteggia's means mountain and Galeazzi's means ground, simple formula

#### The approximate ages of the appearance of the secondary ossification centers around the elbow joint are: reference Gray's anatomy Capitulum-

- -1 year
- Head (of radius)--5 years
- Medial epicondyle--5 years
- Trochlea--11 years
- Olecranon--12 years
- Lateral epicondyle -13 years

#### Abduction of Shoulder Joint

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#### 0-15":

Chapter 1

Accomplished by the supraspinatus muscle——Suprascapular nerve

#### 15°-90°:

- The major function of the deltoid muscle is abduction of the arm beyond the initial 15° accomplished by the supraspinatus muscle.
- Nerve supply of deltoid is Axillary nerve

#### 90°-180°:

- Overhead abduction use for combing hair etc.
- Trapezius:
  - Powerful elevator of the scapula, rotate the scapula during abduction of humerus above horizontal
  - ✓ Supplied by spinal part of the accessory nerve
  - Spinal part of accessory nerve can damage in neck surgery
- Serratus anterior
  - ✓ Supplied by Long thoracic nerve
  - ✓ Commonly damage in mastectomy

#### Loss of the whole abduction:

It is due to damage to upper trunk (Suprascapular nerve) and posterior cord (Axillary nerve) of brachial plexus

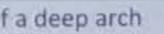
#### S-I-t-S Muscles

- All insert on greater tuberosity except subscapularis which inserts on lesser tuberosity of humerus
- Supraspinatus is the only muscle in rotator cup which causes abduction instead of rotation
- Small t means minor
- Action---ALL Medial rotator------Mnemonic
  - ✓ Supraspinatus

    ——Abduction

    ——Most common rotator cuff injury
  - ✓ Infraspinatus
    ——Lateral rotation
  - ✓ Teres minor -----Lateral rotation
  - ✓ subscapularis------Medial rotation

#### **Carpal Tunnel Syndrome**



- . The carpal tunnel is located at the wrist and is anteriorly composed of a deep arch
- The carpal tunnel is made medially by the bottom of the carpal arch and it is made laterally by the tubercles of the scaphoid as well as trapezium

#### The constitute that travel through carpal tunnel:

- · The median nerve
- The 4 tendon of the flexor digitorum profundus
- The 4 tendon of the flexor superficialias
- The tendon of the flexor pollicis longus

#### Risk factors:

- Occur in myxedema
- May occur in pregnancy

- Obesity
- Female gender
- Genetic predisposition
- Aromatase inhibitor use

#### Clinical features:

- Usually affecting people between the ages of 40 and 60 especially ladies
- Pain and paraesthesia in the radial 3 and a half digits of the hand
- Night pain is common and is relieved by shaking the hand
- Cause motor weakness or paralysis
  - ✓ Paralysis of muscle of the thumb
  - ✓ Atrophy or wastage of muscle of thenar eminence---muscle at the base of thumb looks flattened. There is no sensory loss over the thenar eminence itself
  - Loss of opposition of the thumb

#### Clinical test:

- Phalen's test: Reproduction of paraesthesia with full wrist flexion
- Tinel's test: Tapping over median nerve produces tingling

## The Bicipital Groove of the Humerus

Lady between Two Major

- \* Teres Major--Attach on the medial side of the bicpital groove
- · Pectoralis Major------- Attach on the lateral side of the bicipital groove
- Latissimus dorsi ———latissimus dorsi inserted in the floor of the bicipital groove
- All these three muscles cause Adduction and Medial rotation

#### **SALT Mnemonic**

- Serratus Anterior muscle
- Long Thoracic nerve---C567-----nerve supply of Serratus anterior
- This the big swinging ,boxer, punching and pushing muscle
- Tested by having patient push against the wall
- Commonly injured during radical mastectomy caused winged scapula and ipsilateral
- Injury cause——winging scapula, Normal elevation at the arm is no longer possible.

## Fracture of Head Of Radius

- A fracture of the head of the radius is a common injury and can cause appreciable morbidity. It is one of the typical injuries that occur with a fall on the outstretched hand
- These fractures typically result in loss of full extension

#### Latissimus dorsi



Upper Limb

- Nerve supply----Thoracodorsal nerve, Blood supply: Thoracodorsal trunk
- Cause downward displacement of glenohumeral ligaments
- Action: It extends the shoulder joint and medially rotates the humerus e.g. folding the arms behind the back or scratching the opposite scapula
- Injury: Patient will be unable to scratch back (dorsum), Climb and swim

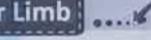
Chapter 1

#### **Clavipectoral Fascia**



- It is a strong sheet of connective tissue that is attached above to the clavicle
- Below, it is split to enclose the pectoralis minor muscle and then continues downward as a Suspensory ligament of the axilla and joins the fascial floor of the armpit, the cephalic vein is present in clavipectoral fascia
- During the axillary node clearance for breast cancer, the clavipectoral fascia is incised and this allows access to the nodal stations
- It is pierced by:
  - ✓ Lateral pectoral nerve
  - Thoraco-acromial artery
  - Cephalic vein
  - ✓ Few lymph vessels

#### Segmental Nerve Supply To Movements and Reflexes in Upper Limb



- · Shoulder:
  - ✓ Flexion/abduction/lateral rotation------C5
- Elbow:

  - ✓ Extension (triceps reflex)------C6, 7,8
- Forearm:
  - ✓ Pronation-----C7.8 ✓ Supination-----C6
- Wrist ------C7.8
- Finger/thumb (long tendon)----- Flexion/Extension------C7,8
- Hand (Small muscle), small finger abductors-----All Movements-----T1
- Active lengthening of flexor ------when a heavy object in hand is lowered the extension at elbow is brought about by active lengthening of flexor. Prime over (agonist) bring about the desired movement. When a prime mover help opposite action by active controlled lengthening against gravity, it is known as action of paradox.

Upper Limb

Wuscles With Drainter Confirm			
		BP BAD For Fun	
*	B	Brachialis	
*	P	Pectineus and Pectoralis major muscle	
*		Bicep femoris	
*	Α	Adductor magnus	
		Antero-lateral papillary muscle	
٠	D	Digastric muscle	
٠		Flexor polices brevis	
0/40	2200		

#### Two differences

-- Flexor digitorum profundus

- · Claw hand -ulnar nerve due to unopposed action of
  - Flexor digitorum profundus
  - Extensor digitorum profundus
- Median nerve: Median nerve lies between;
  - Flexor digitorum profundus
  - Flexor digitorum superficialias

Pattern Of Muscle Wasting In Hand		
Median nerve palsy (C8)		
Ulnar nerve (T1)		
Ulnar nerve (T1)		

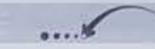
The intrinsic muscles of hand can be remembered using the mnemonic, "A OF A OF A" for, Abductor pollicis brevis, Opponens pollicis, Flexor pollicis brevis (the three thenar muscles), Adductor pollicis, and the three hypothenar muscles, Opponens digiti minimi, Flexor digiti minimi brevis, Abductor digiti minimi.

# Common Nerve Injury In Various Conditions

- Most common nerve in supracondylar fracture: Anterior interosseous nerve (AIN), a branch of
- Most common nerve injure in General anesthesia: Ulnar nerve
- Most common nerve in lithotomy position: Common Peroneal Nerve
- The most common nerve that is injured with knee joint dislocation is common peroneal nerve
- The most common nerve injury after total knee arthroplasty: Common peroneal nerve
- Most common nerve injury in monteggia fracture: Posterior interosseous nerve (PIN), a branch of
- Most common nerve injury in tourniquet application: in Upper limb: Radial nerve and in lower
- ❖ Formant's sign: Asses for ulnar nerve palsy, adductor pollicis muscle function tested



#### Upper limb dermatomes



Dermatomes of the upper limbs are innervated by spinal nerves C5-T2. Here, the organization of dermatomes is complex because of how the upper limbs bud in embryonic development.

- . C5 anterior skin below the clavicles spreading over the lateral aspect of the upper limb, posterior skin around the base of the neck
- \* C6 shoulders and longitudinally down the middle posterior aspect of the upper limb, radial side of the hand, thumb
- · C7 hand, middle finger
- \* C8 ulnar side of the hand, ring finger, and little finger
- T1 level of the infraclavicular fossa, extending to the medial aspect of the forearm
- \* T2 anterior and posteriorly extends at the level of the upper axilla and medial and upper aspect of the arm
- No skin supply-----C1
- \* Neck-----C3
- Infraclavicular region (to manubriosternal junction)------C4
- \* Bicep jerk------C6
- \* Triceps jerk-----C7
- \* Clavicles-----C5
- Level of nipples-----T4
- Lateral side of upper limb-----C5,6
- Medial side of upper limb------C8,T1

Sensory Distribution Of The Nerve Supply To The Hand		
Ulnar	Little finger and ulnar half of the ring finger	
Median	Thumb, index, middle and radial half of the ring finger	
Radial	Base of the thumb on dorsum of the hand	

Upper Limb



#### **Quadrangular Space**

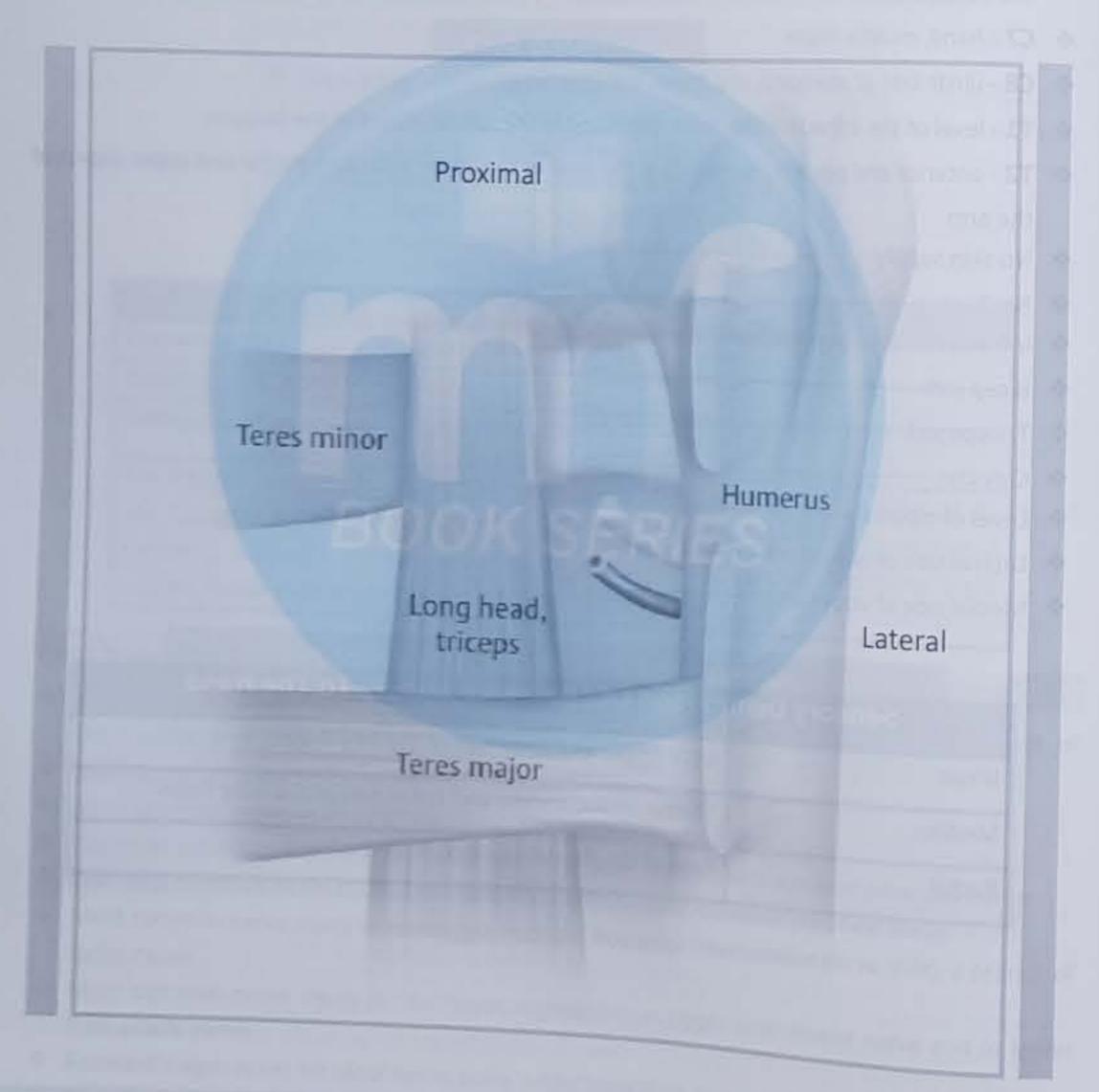


#### Contents:

- Axillary nerve
- Posterior circumflex humeral vessels

#### Boundaries:

- Superiorly: Subscapularis and capsule of the shoulder joint.
- · Inferiorly: The teres major muscle
- Medially: The long head of the triceps
- Laterally: The surgical neck of the humerus



# THORAX

2

#### Trachea



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- The trachea is the continuation of the larynx and begins at the lower border of the cricoid cartilage in the level of C6 vertebra, about 5 cm above the jugular notch and end at T5 (Reference: RJ LAST's Anatomy 12<sup>th</sup> edition P.196)
- There are 16-20 incomplete rings of C-shaped hyaline cartilage, arranged one above the other on the anterior aspect of the trachea.
- The gap between Posterior end is filled with Trachialis muscle, contraction of Trachialis decrease the tracheal diameter
- Size of the trachea in neonate-4 cm and adult 10 cm
- Laryngotracheal bud occurs during 4<sup>th</sup> weeks
- The shape of thorax is varies with age. In newborn infant, the thorax is round when view from above, but increasing with ages it become more oval and appears flatter anteriorly and posteriorly. It is also important to note that the spine of new born is C-shaped with one curve
- \* Epithelium: Pseudostratified columnar ciliated epithelium with goblet cell
- Trachea divides into right and left primary bronchi at the superior border of the fifth thoracic vertebra, the T5

#### / Importance of Carina:

- ✓ It's a keel-like ridge in the lumen in the bifurcation of the trachea or <u>Anterior-posterior</u> cartilage at the bifurcation of trachea
- ✓ The mucosa of trachea over the <u>carina is most sensitive</u>. The cough reflex is generally started here, which helps to clear sputum.

#### Tracheostomy:

- ✓ The most common nerve damage during Tracheostomy is recurrent laryngeal nerve (RLN)
- ✓ Most common vein damage during Tracheostomy is inferior thyroid vein.
- ✓ The most common cause of heavy bleeding during Tracheostomy anterior jugular vein
- ✓ Tracheostomy cuts down dead space by 30-50%
- ✓ The ideal site for Tracheostomy in adult---3<sup>rd</sup> and 4<sup>th</sup> tracheal ring, (adult 34) tracheal
- ✓ Site of Tracheostomy in children-----2<sup>nd</sup> and 3<sup>rd</sup> tracheal ring children, space C2 (23)
- ✓ During Tracheostomy one should not injured 1st tracheal ring
- ✓ During Tracheostomy heat loss by evaporation
- ✓ Tracheostomy is of no benefits if the lesion is at the level of the carina

THORAX

#### Relations:

#### ✓ Anterior:

- o Arch of aorta
- Brachiocephalic trunk and left common carotid artery
- Left brachiocephalic vein
- Deep cardiac plexus

#### ✓ Posterior:

- o Esophagus
- Vertebral column
- Left recurrent laryngeal nerve--- it ascends between trachea and esophagus

#### ✓ To the right: lateral to the trachea

- Right vagus nerve (close contact)
- Right lung and pleura
- Azygos vein

#### To the left: lateral to the trachea

- Left vagus nerve (close contact)
- o Arch of aorta
- Left common carotid artery
- Left subclavian vein
- Left phrenic nerve

# Vagus nerve Recurrent laryngeal Left Carotid artery - Left Subclavian artery

#### Trachea deviation:

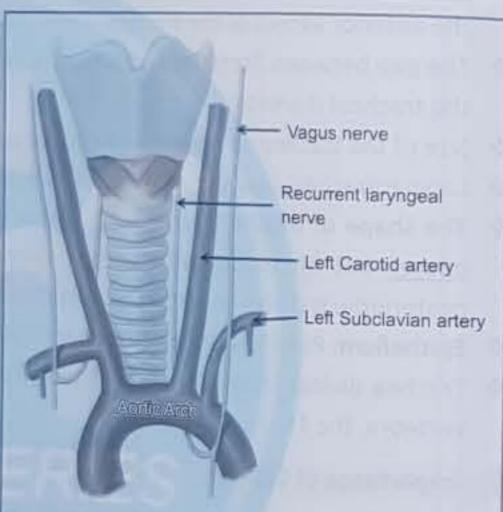
- ✓ IpSilateral: Collapse and fibrosis, Spontaneous Pneumothorax
- ✓ ConTralateral: Tension Pneumothorax

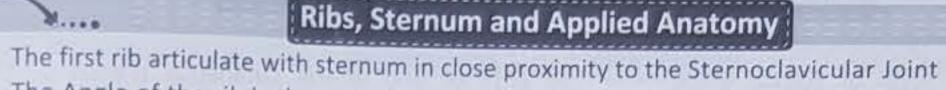
#### Blood Supply of trachea:

- ✓ Upper 2/3 trachea: inferior thyroid artery
- Lower 1/3: branch of the bronchial artery
- ✓ Venous drainage: inferior thyroid plexus

#### Merve supply:

- ✓ Nerve supply of trachea is from Vagi and recurrent laryngeal nerves
- ✓ Sympathetic nerves supply the Trachialis muscle





- The Angle of the rib is the most common site of rib fracture
- Sternum is the most common site for marrow biopsy
- The body, also called the blade or Gladiolus, is right in the middle of the sternum
- The Sternum body ossify at age of 25

#### Sternal angle:

Chapter 2

- The sternal angle (also known as the angle of Louis or manubriosternal junction) is the synarthrotic joint formed by the articulation of the manubrium and the body of the sternum
- ✓ Union of manubrium and body at 2<sup>nd</sup> rib
- ✓ The sternal angle can be palpated at the T4 vertebral level.
- ✓ Structure at the level of the angle of Louis: 2<sup>nd</sup> costal cartilage, arch of the aorta, trachea, pulmonary trunk bifurcation
- There are 12 pairs of ribs
- True ribs: The upper seven are attached anteriorly to the sternum by their coastal cartilage
- False ribs: The 8th, 9th and 10th pairs of rib attached to each other and to the 7th ribs by means of their costal cartilage and small synovial joint
- Floating ribs: The 11<sup>th</sup> and 12<sup>th</sup> pairs have no anterior attachment
- Cervical rib: A rib arising from the anterior tubercle of the transverse process of the 7th cervical vertebra. May be connected to the first rib by a fibrous band, or may articulate with the first rib, which causes pressure on the lower trunk of brachial plexus and the subclavian artery
- Endothoracic fascia: Thin layer of loose connective tissue that separates the parietal pleura from the thoracic wall.

#### Suprapleural membrane:

- ✓ Eponymously known as Sibson's fascia
- ✓ The suprapleural membrane is the thickening of Endothoracic fascia.
- ✓ It attaches to the internal border of the first rib and the transverse processes of vertebra C7.

#### Lavers of Thoracic Wall, From External To Internal



- Skin
- Superficial fascia

2 ....

- External intercostal muscle
- Internal intercostal muscle
- Intercostal vein, artery, nerve
- Innermost intercostal muscle
- Endothoracic fascia
- Parietal pleura
- Pleural cavity
- Visceral pleura
- Finally, reach lungs

THORAX

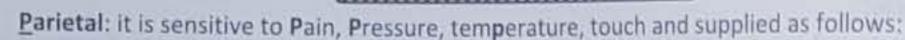
Chapter 2

### Skin innervation of the chest wall and referred pain

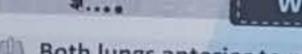
Above the level of the sternal angle-----Supraclavicular nerve (C3-C4)

- Below the level of sternal angle-----The anterior and lateral cutaneous branch of the intercostal nerve
- -The posterior rami of the spinal nerves Posteriorly-----

#### Pleura



- Costal pleura is by-----Completely supplied by Intercostal nerve.
- Mediastinal pleura by------ Completely supplied by Phrenic nerve.
- Diaphragmatic pleura-----Partially supplied by Phrenic nerve. Supplied over the dome by phrenic nerve and around the periphery by the lower six intercostal nerve
- Visceral pleura: Covering the lung and is sensitive to stretch only, it receives an autonomic nerve supply from the pulmonary plexus
- Negative intrapleural pressure is due to lymphatic drainage of pleura



# Within each root and located in the hilum are:

- Both lungs anterior to posterior
  - ✓ Pulmonary veins
  - A pulmonary artery
  - Bronchus (left main bronchus on the left side, and eparterial, and hyparterial bronchus on the right side).
- Right lung----superior to inferior
  - Pulmonary artery
  - Eparterial bronchus
  - Hyparterial bronchus
  - ✓ Pulmonary veins
- left lung----superior to inferior
  - Pulmonary artery
  - ✓ Principal bronchus
  - ✓ Pulmonary veins
- Generally, the pulmonary artery is superior at the hilum, the pulmonary veins are inferior, and
- The difference in the arrangement of structures from above downwards on the 2 sides is because right main bronchus before going into the lung at hilum splits into 2 lobar bronchi, the upper lobar bronchus enters above the pulmonary artery (eparterial bronchus) and lower lobar bronchus enters below the pulmonary artery (hyparterial bronchus).
- A thin blade-like fold of pleura projects inferiorly from the root of the lung and extends from the hilum to the mediastinum. This structure is the pulmonary ligament. It may stabilize the position of the inferior lobe and may also accommodate the down-and-up translocation of structures in

The right lung is normally a little larger than the left lung because the middle mediastinum, containing the heart, bulges more to the left than to the right.

\* The pulmonary arteries deliver deoxygenated blood to the lungs from the right ventricle of the heart. Oxygenated blood returns to the left atrium via the pulmonary veins.

- Pulmonary veins are the major venous drainage of lungs
- Normal lung pleura is composed of fibrous connective tissue lined by mesothelium.

Right Lung	Left Lung
The right lung has three lobes and two fissures. Normally, the lobes are freely movable against each other because they are separated, almost to the hilum, by invaginations of visceral pleura. These invaginations form the fissures: ✓ The oblique fissure separates the inferior lobe (lower lobe) from the superior lobe and the middle lobe of the right lung; ✓ The horizontal fissure separates the superior lobe (upper lobe) from the middle lobe.	

Some Important	t Relation of Lung
Structure arch over the left lung	Arch of aorta
Structure arch over the right lung	Azygos vein
Structure anterior to the root of the lung	Phrenic nerve
Structure posterior to the root of the lung	Vagus nerve
Left recurrent laryngeal nerve	Loops around the aortic arch behind the ligamentum arteriousm
Right recurrent laryngeal nerve	Hook around the right subclavian artery
Both right and left recurrent laryngeal nerve	in the groove between esophagus and trachea
Structure winding around left bronchus is	Aortic arch
Structure not compressed in aortic aneurysm is	Phrenic nerve
Lower respiratory components sympathetic supply via	T2-T4
	e Muscle Relation
<ul> <li>❖ Structure Anterior to anterior scalene muscle</li> <li>✓ Phrenic nerve</li> <li>✓ Thyrocervical trunk and Vagus nerve</li> <li>✓ Subclavian vein</li> <li>✓ Anterior scalene muscle separate</li> </ul>	muscle  ✓ Subclavian artery ✓ Brachial plexus

subclavian vein from subclavian artery

#### **Bronchial Tree**

After passing through the nasal passages and pharynx, where it is warmed and takes up water vapor. the inspired air passes down the trachea and through the bronchioles, respiratory bronchioles, and alveolar ducts to the alveoli, where gas exchange occurs. Between the trachea and the alveolar sacs. the airways divide 23 times. The first 16 generations of passages form the conducting zone of the airways that transport gas from and to the exterior. They are made up of bronchi, bronchioles, and terminal bronchioles. The remaining seven generations form the transitional and respiratory zones where gas exchange occurs; they are made up of respiratory bronchioles, alveolar ducts, and alveoli. These multiple divisions greatly increase the total cross-sectional area of the airways, from 2.5 cm2 in the trachea to 11,800 cm2 in the alveoli. Consequently, the velocity of airflow in the small airways declines to very low values. The arrangement is given below

- The Trachea divides into principal or primary bronchus—one on left & one on right side
- The Main bronchus divide into lobar (secondary) bronchus---3 on right and 2 on left side
- Segmental
- Tertiary bronchus
- Terminal bronchus
- Lobular bronchioles
- Terminal bronchioles
- Respiratory bronchioles

#### Alveolar ducts:

- ✓ Lined by Simple Cuboidal or simple squamous epithelium
- Bound entirely by alveoli, the alveoli protruded from their lumens and their openings are separated by a very small segments or knobs of smooth muscles

#### Alveolar sac:

Each has man alveoli opening into its lumen and without any wall and muscles between

#### Zone of lungs

#### Zone 1-----Area of zero flow

- When alveolar pressure is greater than pulmonary capillaries pressure, capillaries remain
- Occurrence: it does not occur in normal lung. It occurs
  - ✓ When pulmonary arterial pressure falls following hemorrhage
  - When a person breaths against higher air pressure as when blowing on a musical

#### Zone 2----area of intermittent flow

- Pulmonary capillaries collapse during diastole (zero blood flow) and open up during systole
- - ✓ It occurs in normal lungs in "Standing position" from 7-10cm above heart's level to

#### Zone 3-----Area of continuous flow

Chapter 2

- When pulmonary capillary pressure is greater than alveolar pressure, capillaries always remain opened and there is continuous blood flow.
- Occurrence: it occurs in the normal lung in;
  - ✓ "Standing position" from 7-10cm below heart level to base of the lung due to the hydrostatic pressure of blood
  - ✓ Laying position

Conducting zone: it has 16 division

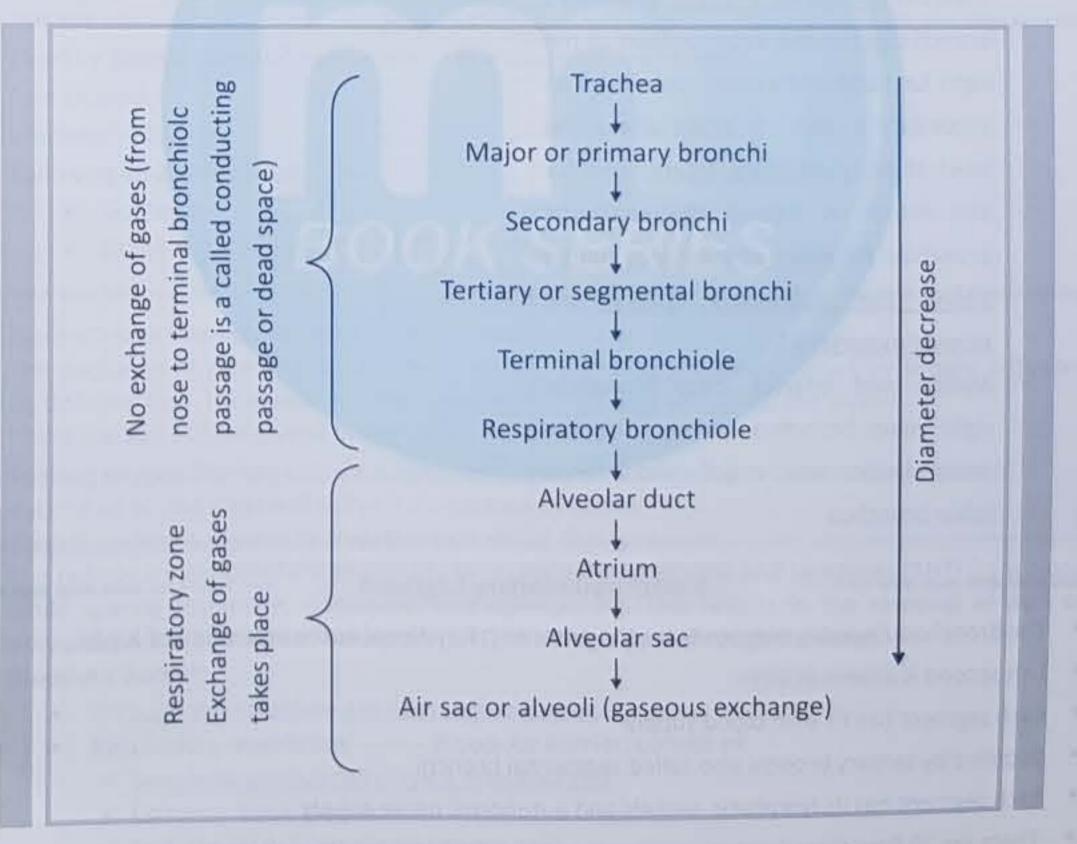
✓ Exercise

#### Functional classification of the respiratory system

- Its main function is to filter, warm, and moisten air and conduct it to the lungs.
- Nasal cavities------Pharynx------Larynx------Trachea------Bronchi-----Bronchioles

#### Respiratory zone: it has 7 terminal division

- It is the main site for gas exchange between air and blood.
- Respiratory Bronchioles-----Alveolar Duct-----Alveolar Sac----Alveoli



**THORAX** 

# Explanation From Primary Bronchus To Alveoli

The trachea bifurcates behind the arch of aorta into:

The right Principal	Main/primary)	Bronchus
	THE PROPERTY OF THE PERSON NAMED IN CO.	

#### Wider

- Shorter
- More vertical
- Length ————1 inch or 2.5 cm

## The Left Principal (Main/Primary) Bronchus

- Narrow
- Longer
- More horizontal
- Length----2 inch or 5cm

#### Three lobes

- ✓ Superior lobar bronchus: Right main bronchus before entering the hilum give the superior lobar bronchus
- The eparterial bronchus (right superior lobar bronchus) is a branch of the right main bronchus given off about 2.5 cm from the bifurcation of the trachea. This branch supplies the superior lobe of the right lung and is the most superior of all secondary bronchi. It arises above the level of the pulmonary artery, and for this reason is named the eparterial bronchus. All other distributions falling below the pulmonary artery are termed hyparterial.
- Middle and inferior lobar bronchus: right main bronchus on entering the hilum divides into middle and inferior lobar bronchus

#### Two lobes:

- ✓ Superior and inferior lobar bronchus:
- ✓ Left main bronchus on entering the hilum divides into superior and inferior lobar bronchus

# **Bronchopulmonary Segment**

- The Bronchopulmonary segments are the anatomic, functional and surgical unit of lungs. Street Square over 1980 and 1980 and
- Each segment has its own blood supply
- Supplied by tertiary bronchi also called segmental bronchi
- Each segment has its lymphatic vessels and autonomic nerve supply
- There are 10 Bronchopulmonary segments in the right lung and 10 in the left lung

- \* Right lung---APA-LM, AMA-LP----10: -----3-2-5
  - Superior lobe: Apical, Posterior, Anterior----3
  - Middle lobe: Lateral, Medial-----2
  - Inferior lobe: Superior(Apical), Medial Basal, Anterior basal, Lateral basal, Posterior basal----5
- ❖ Left lung---10

Chapter 2

- Superior lob: Apical, Posterior, Anterior, Superior lingular, Inferior lingular
- Inferior lobe: Superior(apical), Medial basal, Anterior basal, Lateral basal, Posterior

#### **Terminal Bronchioles**

- Lined by Simple cuboidal epithelium
- No mucinous cell and no goblet cell

NAME AND POST OFFICE ADDRESS OF TAXABLE PARTY.

- No cartilage, this absence of cartilage in terminal bronchioles differentiates it from conducting zone which having cartilage in their wall.
- Terminal bronchioles signifies the end of the conduction zone
- Contain Clara cell--function of Clara cell
  - ✓ Reserve cells
  - ✓ Produce surfactant also

#### **Respiratory Bronchioles**

- Lined by Simple Cuboidal epithelium or low columnar epithelium
- Non-ciliated
- Diameter---0.5mm
- Following structure absent:
  - ✓ Goblet cell

✓ Gland and Cartilage

#### Alveoli

- Gas exchange takes place at the level of alveoli
- . The exchange of gases (O2 & CO2) between the alveoli & the blood occurs by simple diffusion. O2 diffusing from the alveoli into the blood & CO2 from the blood into the alveoli
- \* There are 300 million alveoli in each lung
- \* Prolong oxygen therapy cause injury to pulmonary alveoli leading to constriction of alveoli
- \* Ascending SCUBA diver will suffer from rupture of alveoli
- Alveoli surface is dry due to Negative interstitial fluid pressure
- . The pulmonary endothelium selectively takes up norepinephrine and serotonin (5HT) from blood while sparing histamine, dopamine, and epinephrine. This results in the removal of 30% of norepinephrine and 98% of serotonin (5HT) in a single pass through the lungs.
- \* Blood-Air Barrier:
  - Through this structure gas exchange take place
  - Respiratory membrane ----- Blood-Air Barrier: consist of
    - ✓ Simple squamous cell (Type 1 Pneumocyte)
    - √ Common Basal lamina
    - ✓ Endothelial cell (simple squamous cell)

THORAX

#### Lung Defense Mechanisms

- The respiratory passages that lead from the exterior to the alveoli do more than serving as gas conduits. They humidify and cool or warm the inspired air so that even very hot or very cold air is at or near body temperature by the time it reaches the alveoli.
- Airway epithelial cells can secrete a variety of molecules that aid in lung defense.
- Secretory immunoglobulins (IgA), collectins (including Surfactant A and D), defensins and other peptides and proteases, reactive oxygen species, and reactive nitrogen species are all generated by airway epithelial cells. These secretions can act directly as antimicrobials to help keep the airway free of infection. Airway epithelial cells also secrete a variety of chemokines and cytokines that recruit the traditional immune cells and others to site of infections.
- Various mechanisms operate to prevent foreign matter from reaching the alveoli. The hairs in the nostrils strain out many particles larger than 10 µm in diameter.
- Most of the remaining particles of this size settle on mucous membranes in the nose and pharynx; because of their momentum, they do not follow the airstream as it curves downward into the lungs, and they impact on or near the tonsils and adenoids, large collections of immunologically active lymphoid tissue in the back of the pharynx.
- Particles 2 to 10  $\mu m$  in diameter generally fall on the walls of the bronchi as the airflow slows in the smaller passages. There they can initiate reflex bronchial constriction and coughing. Alternatively, they can be moved away from the lungs by the "mucociliary escalator."
- The epithelium of the respiratory passages from the anterior third of the nose to the beginning of the respiratory bronchioles is ciliated. The cilia are bathed in a periciliary fluid where they typically beat at rates of 10-15 Hz.
- On top of the periciliary layer and the beating cilia rests a mucus layer, a complex mixture of proteins and polysaccharides secreted from specialized cells, glands, or both in the conducting airway. This combination allows for the trapping of foreign particles (in the mucus) and their transport out of the airway (powered by ciliary beat). The ciliary mechanism is capable of moving particles away from the lungs at a rate of at least 16 mm/min.
- When ciliary motility is defective, as can occur from smoking, other environmental conditions, or genetic deficiency, mucus transport is virtually absent. This can lead to chronic sinusitis, recurrent

# Structure damage in Penetrating Injury to chest ✓ 4<sup>th</sup> intercostal space to the left of sternum——intercostal membrane

- ✓ 5<sup>th</sup> intercostal space to the left of sternum——————————Intercostal muscle 6<sup>th</sup> intercostal space to the right of sternum————Right atrium

#### Intercostal Spaces

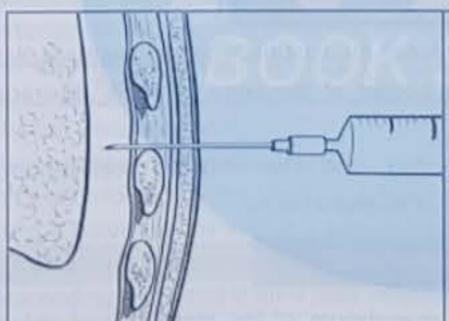
#### 1) Blood supply

Each intercostal space contains a large single posterior intercostal artery and two small anterior intercostal arteries.

- Anterior intercostal arteries:
  - ✓ The anterior intercostal arteries of the first six spaces are branches of the internal thoracic artery, which arises from the first part of the subclavian artery.
  - ✓ The anterior intercostal arteries of the lower spaces are branches of the musculophrenic artery, one of the terminal branches of the internal thoracic artery.
- Posterior intercostal arteries:
  - ✓ The posterior intercostal arteries of the first two spaces are branches from the superior intercostal artery, a branch of the Costocervical trunk of the subclavian artery.
  - ✓ The posterior intercostal arteries of the lower nine spaces are branches of the descending thoracic aorta

#### 2) Neurovascular bundle

- The inferior border of the superior rib forms the "Coastal groove" which accommodates Neurovascular bundle. The intercostal drainage tube should be inserted along the superior surface of the inferior rib (lower border of intercostal space). Must enter the chest OVER the rib, not under
- From superior/above to inferior/downward: intercostal Vein, intercostal Artery and intercostal Nerve-----VAN
- Intercostal nerve is at higher risk of injury
- Neurovascular bundle is Located between internal and innermost layer



Neurovascular bundle normally lies along the lower border of the rib / upper part of intercostal space So, insert needle into the upper border of the rib and not into the lower border of the rib / Insert the needle in the lower part of intercostal space and not to upper part of the intercostal space

#### 3) Intercostal muscles:

Intercostal muscle form the wall proper of the thorax

#### 4) Bronchial artery:

- Bronchial artery one on the right side and 2 on the left side
- The left bronchial arteries (superior and inferior) usually arise directly from the thoracic aorta.
- The single right bronchial artery usually arises from any number of the right intercostal arteries mostly the third right posterior
- Bronchial artery arises at the level of T5-T6

#### Chapter 2

#### 5) Intercostal nerve

- The intercostal nerves are part of the somatic nervous system, and arise from the anterior rami of the thoracic spinal nerves from T1 to T11 and supply Subcostalis Muscle.
- intercostal nerves are distributed chiefly to the thoracic pleura and abdominal peritoneum and differ from the anterior rami of the other spinal nerves in that each pursues an independent course without plexus formation.
- The first two nerves supply fibers to the upper limb in addition to their thoracic branches
- \* The next four are limited in their distribution to the walls of the thorax; the lower five supply the walls of the thorax and abdomen.
- \* The 7th intercostal nerve terminates at the xiphoid process, at the lower end of the sternum.
- The 10th intercostal nerve terminates at the umbilicus.
- The twelfth (subcostal) thoracic is distributed to the abdominal wall and groin.
- The lateral cutaneous branch of the second intercostal nerve does not divide, like the others, into an anterior and a posterior branch; it is named the intercostobrachial nerve.

#### Intercostobrachial nerve:

- The intercostobrachial nerve is a <u>lateral cutaneous branch of the second intercostal</u> nerve that supplies sensation to the skin of the axilla. It leaves the second intercostal space at the midaxillary line and subsequently pierces the Serratus anterior muscle to enter the subcutaneous tissues of the axilla.
- It traverses the axillary lymph nodes and is often divided during axillary surgery.

#### Mediastinum

- The mediastinum is divided into superior and inferior mediastinum by an imaginary plane passing from the sternal angle anteriorly to the lower border of the body of the 4<sup>th</sup> thoracic vertebra
- The inferior mediastinum is further subdivided into the middle mediastinum, anterior mediastinum and posterior mediastinum: Detail of all given below

#### **Superior Mediastinum**

- The superior mediastinum is posterior to the manubrium of the sternum and anterior to the
- Its superior boundary is an oblique plane passing from the jugular notch upward and posteriorly
- Inferiorly, a transverse plane passing from the sternal angle to the intervertebral disc between Laterally, it is bordered by the Mediastinal part of the parietal pleura on either side.
- The superior mediastinum is continuous with the neck superiorly and with the inferior

- The major structures found in the superior mediastinum include:
  - Thymus,

Chapter 2

- Right and left brachiocephalic veins,
- Superior vena cava,
- Arch of the aorta---- with its three large branches,
- Vagus nerves-----Present in close contact with trachea on its right side
- Trachea,
- Esophagus,
- Phrenic nerves,
- Left recurrent laryngeal branch of the left vagus nerve,
- Thoracic duct

#### Middle Mediastinum



- The middle mediastinum is centrally located in the thoracic cavity.
- It contains the pericardium, heart, origins of the great vessels, various nerves, and smaller vessels.
- Cyst most commonly found in the middle mediastinum

#### **Anterior Mediastinum**



- The major structure in the anterior mediastinum is a portion of the thymus. Also present are fat, connective tissue, lymph nodes, Mediastinal branches of the internal thoracic vessels, and sternopericardial ligaments, which pass from the posterior surface of the body of the sternum to the fibrous pericardium.
- Infection from pretracheal fascia can spread into the anterior mediastinum
- The most common tumor of the anterior mediastinum is Thymoma

#### Posterior Mediastinum



- The posterior mediastinum is posterior to the pericardial sac and diaphragm and anterior to the bodies of the mid and lower thoracic vertebrae
- its superior boundary is a transverse plane passing from the sternal angle to the Intervertebral disc between vertebra TIV-V;
- its inferior boundary is the diaphragm;
- laterally, it is bordered by the Mediastinal part of parietal pleura on either side;
- Superiorly, it is continuous with the superior mediastinum.
- Major structures in the posterior mediastinum include: DATES
  - Descending aorta and their 9 post intercostal branches
  - Azygos and hemiazygos vein
  - Thoracic duct-----found in the both superior and posterior mediastinum
  - Esophagus
  - ✓ Sympathetic trunk/ganglia

#### **Naseem Sherzad High-Yield Points**

- . The most common tumor in the posterior mediastinum is Neurogenic tumor
- Most common Mediastinal mass is Neurogenic tumor
- Most common Mediastinal mass in children is Neurogenic tumor
- Most common malignant mass of mediastinum is lymphomas
- Most common anterior Mediastinal mass is Thymoma

#### 1) Inspiration: 2 cycle, active process

#### Quite breathing:

- During normal quite respiration, only 3-5% of the total energy expended by the body is required for pulmonary ventilation
- · Diaphragm:
  - ✓ Most Powerful and major inspiratory muscle
  - ✓ Contraction of diaphragm increase in vertical thoracic diameter
  - ✓ Increase Lung capacity by 2/3<sup>rd</sup>

#### Exercise

#### External intercostal muscle

- ✓ Increase in the transverse diameter by elevation of ribs
- ✓ A man with RTA having multiple rib fracture and his abdomen is moving with breathing, the muscle which involved is external intercostal muscle
- Accessory muscle
  - SCM---- Elevate sternum
  - Scalenus groups-----Elevate upper ribs

#### 2) Expiration:

- ✓ 3 cycles , under resting condition expiration is normally a passive process
- Quite breathing
  - Normal quite expiration is brought about by contraction/recoil of Elastic tissue in thoracic and lung wall
  - The Major part of energy utilize during breathing is to overcome elastic recoil of lungs.

#### Exercise

- Internal intercostals muscle (pull ribs downward and inward)
- Abdominal muscle:
  - Rectus abdominis (main muscle)
  - Transverses abdominis
- ✓ Internal and external oblique muscle

#### 3) Elastic Recoil of the lung:

- It is a tendency of a stretched object to return to its original shape
- Recoil, as a force, always acts to collapse the lung, Almost 70% of work of breathing is to
- Surfactant account for 70% of the elastic recoil
- Recoil tendency of lungs: lungs have a natural elastic tendency to collapse; this is called recoil
- 5) Work of breathing:
  - It is the amount of energy required to ventilate the lung and overcome all kinds of
  - Work of breathing = Pressure x Volume

Chapter 2

THORAX

#### Naseem Sherzad High-Yield Points

- Vertical diameter:
  - Increase by diaphragm
- Transverse diameter
  - Bucket handling
  - Increase by external intercostals muscles
- Anteroposterior diameter
  - Hand pump handling
  - Increase by external intercostals muscles

#### Diaphragm

- 1) The diaphragm is a thin musculotendinous structure that fills the inferior thoracic aperture and separates the thoracic cavity from the abdominal cavity It is attached peripherally to:
  - The xiphoid process of the sternum;
  - The costal margin of the thoracic wall
  - The ends of ribs XI and XII
  - Ligaments that span across structures of the posterior abdominal wall
  - Vertebrae of the lumbar region
- 2) Innervation:
  - ♦ Motor: Right and left Phrenic nerves—(C345)-----(C4 = largest contribution)
  - Sensory:
    - ✓ The parietal pleura and the peritoneum covering the central surface of the diaphragm are from phrenic nerve
    - ✓ The Periphery of the diaphragm from lower six intercostal nerve
- 3) Venous drainage: Venous drainage of the diaphragm is by veins that generally parallel the arteries. The veins drain into:
  - The brachiocephalic veins in the neck;
  - The Azygos system of veins; or
  - Abdominal veins (left suprarenal vein and inferior vena cava)
- 4) Structure perforating diaphragm:
  - V------A----From Anterior to Posterior
  - V-----8-----Phrenic, IVC at 8 level-----pIN8----PINT
  - O-----Left gastric artery , Esophagus, Vagus nerve and Esophageal vein---------LOVE
  - A-----Azygos vein , Thoracic duct , Aorta-----ATA
  - Other structure which also passes through this opening:
    - ✓ Sympathetic splanchnic nerve
    - ✓ Superior epigastric vessels
    - ✓ Sympathetic trunk

# Embryology of Thorax and GIT

- Diaphragm Develop from septum transversum on 8-12 week
- The Physiological hernia is 90-degree counter-clockwise and occurs on 4-6 weeks

#### Congenital diaphragmatic hernia(CHD):

- It is caused by the <u>failure of the pleuroperitoneal membrane</u> to develop or fuse with the other compartments of the diaphragm.
- It is associated with lung aplasia
- Respiratory embarrassment is the key presentation with an empty feeling of the abdomen

#### Bochdalek hernia:

 The most common type of congenital diaphragmatic hernia (CHD) is a Bochdalek hernia. Also known as a postero-lateral diaphragmatic hernia

#### Morgagni hernia:

- It is classically known as anterior diaphragmatic hernia, is on the right anterior side
- It is characterized by herniation through the foramina of Morgagni. It is associated with lung hypoplasia

#### 6) Diaphragmatic eventration:

- Upward displacement of abdominal contents secondary to a congenitally thin hypoplastic diaphragm
- It is due to incomplete muscularization of the diaphragm
- Failure of muscular development of all or part of the diaphragm, complete almost always on the left side while partial is common on the right side

#### Omphalocele:

- An Omphalocele is caused by an opening (defect) in the middle of the abdominal wall at the bellybutton (umbilicus). The skin, muscle, and fibrous tissue are missing. The intestines spill (herniate) out through the opening and are covered by a thin sac.
- The umbilical cord is in the center of the defect.
- An Omphalocele commonly occurs along with other birth defects (such as heart defects and kidney defects) and with specific genetic syndromes (such as Down syndrome, Trisomy 18,

#### Gastroschisis:

- Gastroschisis also is an abnormal opening of the abdominal wall,
- In Gastroschisis, the opening is near the belly button (usually to the right) but not directly
- Like in Omphalocele, the opening allows the intestines to spill out but unlike Omphalocele, the intestines are not covered by a thin sac. It occurs due to a defect in the failure of

#### 9) Imperforate anus:

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- Imperforate anus is a type of anorectal malformation
- It is due to failure of decent of the Urorectal septum
- Anorectal malformation can be associated with other anomalies such as esophageal atresia and cardiac anomalies

#### 10) Rotation of midgut:

- Midgut loop has cranial limb and caudal limb
- Mid gut loop rotates around the Superior mesenteric artery
- Midgut loop rotates first 90 degrees to bring the cranial limb to the right and caudal limb to left during the physiological hernia
- The cranial limb of midgut loop elongate to form the intestinal coiled loops (jejunum and ileum)
- This rotation is counterclockwise and it is completed to 270 degrees, so after reduction of physiological hernia it rotates to about 180 degrees

#### Landmarks And Applied Anatomy

#### Midaxillary line

 In Midaxillary line all three lobe of lung can be auscultated The biopsy site for liver is typically between the seventh and eighth intercostal space at the mid-axillary line, which is the point of maximal dullness.

#### **Tension Pneumothorax:**

- Needle decompression for emergency treatment of tension Pneumothorax: insertion of a large bore needle into the Mid-clavicular line in the 2nd intercostal space
- Followed by insertion of chest tube: anterior-axillary line in 5th Intercostals space (ICS)

#### Pericardiocentasis:

 A needle is inserted into the pericardial cavity through the fifth intercostal space left to the sternum

#### Hyper-resonance area:

Right mid-clavicular line in T2-T4 level

#### The Area normally resonant to percussion:

Second to 4<sup>th</sup> intercostal space on the right

#### Resonance area from back:

3<sup>rd</sup> till 8<sup>th</sup> ribs

#### Nipple:

4<sup>th</sup> ICS, 10cm from the midline

#### Oblique fissure of lung:

T3-T6

#### **Lines of Orientation**

Several imaginary lines are sometimes used to describe surface locations on the anterior and

- posterior chest walls. Midsternal line: Lies in the median plane over the sternum
  - Midclavicular line: Runs vertically downward from the midpoint of the clavicle
  - Anterior axillary line: Runs vertically downward from the anterior axillary fold
  - Posterior axillary line: Runs vertically downward from the posterior axillary fold
  - Midaxillary line: Runs vertically downward from a point situated midway between the anterior and posterior axillary folds
  - Scapular line: Runs vertically downward on the posterior wall of the thorax, passing through the inferior angle of the scapula (arms at the sides)

Percussion Notes		
Туре	Detected over	
Resonant	✓ Normal lung	
<ul> <li>Hyperresonant</li> </ul>	✓ Pneumothorax and emphysema	
* Dull	✓ Pulmonary consolidation ✓ Pulmonary collapse ✓ Severe pulmonary fibrosis	
Stony Dull	✓ Pleural effusion ✓ Haemothorax	

#### **Thoracic Duct**

#### Right Lymphatic Duct

- Largest lymphatic vessels
- Also called left lymphatic duct
- Length---38-45cm
- Transport up to 4 liters of lymphatic fluid each day
- 75% of lymphatic fluid from the entire body
- Begin in front of L1 as a dilated sac the cisterna chyli
- Formed by left and right lumbar trunk and intestinal trunk
- Drain into confluence of left subclavian vein and left internal jugular vein
- Having a valve
- Pass through the posterior mediastinum
- Does not drain right side of the body
- Trauma to thoracic duct causes chylopericardial effusion

- The right jugular, subclavian and bronchomediastinal trunk, which drain the right side of the head and neck, the right upper limb and the right side of the thorax, respectively may join to form the right lymphatic duct
- This common duct if present, is about 0.5 inch long and open into the beginning of the right brachiocephalic vein
- Alternatively, the trunk open independently into the great veins at the root of the neck

#### Chapter 2

THORAX

#### **Brachiocephalic Vein**

- Brachiocephalic vein is formed by the union of the internal jugular vein and subclavian vein behind the Sternoclavicular joints (Behind the medial/sternal end of the clavicle)
- SVC is formed by the union of the right and left brachiocephalic veins

	Right Brachiocephalic Vein		Left Brachiocephalic Vein
	Vertical course		Oblique course
*	Shorter, 1 inch	•	Longer, 2 and half inch
	On its right side lies phrenic nerve and on its left side lies innominate artery	* *	Anterior: Manubrium  Posteriorly: branch of the aortic arch, trachea and left vagus nerve
	Note: in obstruction of the upper inferior vena cava, the Azygos and hemiazygos veins and vertebral plexus are the main collateral channels maintaining venous circulation		Inferiorly: the arch of aorta  Receives:  Inferior thyroid vein Thoracic duct Inferior thymic vein Superior intercostal vein

#### Azygos (unpaired) Vein

#### Formed by the union of right ascending lumbar vein and the right costal vein

- It has no symmetrically equivalent vein on the left side of the body.(unpaired)
- Empty into the posterior surface of SVC inside the pericardium
- If IVC is blocked just above the emergence of Azygos vein, blood will divert into left ascending lumbar vein

#### Tributaries:

- √ 8 lower intercostal vein
- ✓ Right superior intercostal vein
- √ Superior and inferior hemiazygos vein
- √ Numerous Mediastinal vein
- ✓ All posterior intercostal vein except Ist vein

#### Hemiazygos Vein (HV)

## Inferior HV

- ✓ Formed by the union of left ascending lumbar vein and the left subcostal vein
- ✓ Turn to the right and join the Azygos vein in front of T9

#### Superior HV:

- ✓ Formed by the union of the 4<sup>th</sup> to the eight intercostal vein
- ✓ It joins the Azygos vein at the level of T7

#### THORAX

# Naseem Sherzad High-Yield Points

- -Apical segment of right lower Foreign body: 

  Supine position—
  - -Basal segment of right lower ✓ Standing position—
  - ✓ Incase of situs Inversus foreign body lodge....into left lower.
- Tumor/foreign body in superior lobar bronchus will affect apical superior Bronchopulmonary segment of lung
- Secondary Tuberculosis: involve Apical and posterior segment of upper lobes because of high ventilation-perfusion ration with elevated alveolar PO2 relative to other zones.
- Primary Tb involve mid/lower lobe
- Pulmonary vein varix (PVV) of congenital origin is an anomalous dilatation of the pulmonary vein with no evidence of increased venous pressure, which fills at the same rate as the normal pulmonary veins and drains into the left atrium with a delay compared to other normal pulmonary veins
- Piriform fossa:
  - ✓ Also called smuggler's fossa (foreign body may lodge here-Fish bones also get stuck here)
  - Pyriform sinus tumors account for 70% of cancer that originates in the hypopharynx
  - Covered by mucous membrane. Beneath the membrane run the internal laryngeal nerve
  - Bounded medially by the aryepiglottic fold, laterally by the thyroid cartilage and thyrohyoid membrane.
- Things that can be seen first on bronchoscopy is right upper lobe
- Aspiration of fluid during fits can be prevented by closure of false vocal cord
- The Right lung is larger than the left lung and is divided by oblique fissure and horizontal fissure into three lobes
- The left lung is divided by oblique fissure into two lobes upper and lower lobes.
- There is no horizontal fissure in the left lung
- Large particles become deposited in the mucus layer that lies within the bronchi.
- TB reactivations most commonly occur at the apex. The site is better oxygenated than elsewhere allowing TB to multiply more rapidly then spread both locally and distantly
- Apex of lung reach 2.5cm above medial one third of the clavicle

#### Thorax and abdomen dermatomes

The dermatomes of the thorax and abdomen are T3-T12. Anteriorly, each is quite evenly spaced, with T1-T9 being near horizontal lines, and T10-T12 having the lower borders dip inferiorly. Posteriorly, each is evenly spaced and oriented as infero-lateral sloped lines from the spine.

- \* T3 anterior and posteriorly extends at the level of the lower axilla
- \* T4 anteriorly at the level of the nipple
- \* T5 anteriorly at the level just inferior to the nipple
- \* T6 anteriorly at the level of the xiphoid process
- T7-T9 evenly distributed anteriorly between T6 and T10 dermatomes
- \* T10 anteriorly at the level of the umbilious
- T11 evenly distributed anteriorly between T10 and T12 dermatomes
- \* T12 anteriorly just superior to the pelvic girdle

# C H A P T E RTHE LUNGS PHYSIOLOGY AND PATHOLOGY

#### **PHYSIOLOGY**

Pulmonary Volume	Pulmonary Capacity
Tidal volume: V <sub>T</sub> 500ml	Inspiratory capacity: 3500ml
✓ It is the volume of air inspired or	✓ It is the combination of tidal volume
expired with each normal breath	and inspiratory reserve volume
Inspiratory reserve volume:	Functional residual capacity: 2300ml
✓ It is an extra volume of air that can be	✓ It is the combination of expiratory
inspired forcefully over and beyond	reserve volume and residual volume or
normal tidal volume	✓ The Volume remaining in the lung
✓ Value3000ml	after expiration of a tidal volume
Expiratory reserve volume:	Vital capacity: 4600ml
✓ It is the extra volume of air that can	
be <u>expired</u> forcefully over and beyond	reserve volume, tidal volume and
value1100 ml	expiratory reserve volume or
✓ Note: The forced expiratory volume in	
1 second (FEV <sub>1</sub> ), commonly used for	
predicating post-up lung function.	capacity or vital capacity
Residual volume: 1200 ml	Total lung capacity: 5800 ml
✓ It is the volume of air that remaining	✓ It is the combination of vital capacit
in lungs after most forceful expiration	10 10 10 10 10 10 10 10 10 10 10 10 10 1

NOTE: Most volumes and capacities can be measured by using a spirometer, but the residual volume and any capacity containing residual volume cannot be measured with a spirometer. TLC and FRC and RV can't be measured using simple Spirometry

Surfactant

Fetus begin to produce surfactant by 24 and 28 weeks and by 35 weeks baby have completed

#### Chemistry of surfactant:

- ✓ Phospholipids: Phospholipids form about 75% of the surfactant. Major phospholipids present in the surfactant is Dipalmitoylphosphatidylcholine (DPPC)or called (dipalmitoyl lecithin, DPL)
- Protein: SP-A (50-70 %); Sp-D: hydrophilic,----SP-B; SP-C: hydrophobic
- lons: mostly calcium ions are present
- ✓ Lecithin-sphyngomyelin (L/S )ratio: Predictor of fetal lung maturity

#### The Function of surfactant:

- \* Surfactant form a macromolecular layer between a water molecule and produce a mononuclear film over the alveolar surface
- It reduces surface tension and increases compliance, increases compliance means that lung and chest wall will expand easily and it will reduce the compliance work means less work will be required to expand the lung and chest wall.
- Another important function of surfactant is its role in defense within the lungs against infection and inflammation. Hydrophilic protein SPA and SPD destroy bacteria and viruses by means of opsonization

#### Clinical Points:

- It is associated with patchy atelectasis and its level decreases in the lungs of the smoker
- Thyroxin and cortisol increase the level of surfactant
- The absence of surfactant in the infants, causes the collapse of the lungs and the condition is called respiratory distress syndrome or hyaline membrane disease. Deficiency of surfactant occurs in adult also and it is called adult respiratory distress syndrome
- Lung maturation in the fetus is regulated by the fetal secretion of cortisol. Treatment of mothers with a large dose of glucocorticoid reduces the incidence of respiratory distress syndrome in infants delivered prematurely. When delivery is anticipated before 34 weeks of gestation I/M Betamethasone, 12 mg followed by an additional dose of 12 mg 12-24
- Surfactant is more important to keep small alveoli patent

Type-I Pneumocyte	Type II D
Squamous "flat" epithelial cell	Cuboidal acid Preumocyte
Cover 90% of total alveolar surface	Cuboidal epithelial cell  More numerous then type-I but cover only  10% of total alveolar surface and
Very thin cytoplasm (to permit gas exchange)	Capable of division:  Reserve for type-I pneumocyte  Because type II pneumocytes function  as alveolar reserved.
Incapable of division	proliferate after lung injury.  Also produce surfactant  Lamellar bodies by E/M

Chapter 3

Definition:

Different types:

The Lungs

#### Dead Space

The volume occupied by air, which does not take part in the gas exchange in the lungs

#### Anatomical dead space:

- ✓ Anatomic dead space is the column of the conducting airways------From nose to terminal bronchioles.
- About 150ml in an average adult or 2.2ml/kg
- Anatomical dead space is constant regardless of circulation.
- ✓ Nitrogen washout (or Fowler's method) is a used for measuring anatomic dead space in the lung during a respiratory cycle, as well as some parameters related to the closure of airways.

#### Physiological dead space or total dead space:

- Alveolar plus anatomical dead space
- Physiological dead space is the part of the tidal volume, which does not participate in gas exchange.
- ✓ In normal personal anatomical dead space is equal to physiological dead space

#### Alveolar dead space:

- In some alveoli, the exchange does not take place due to poor blood supply is called alveolar dead space. Or
- ✓ The difference between physiological and anatomical dead space is called alveolar. dead space.
- ✓ It is increased by:
  - General anesthesia
  - o IPPV
  - O PEEP
  - Hypotension
- ✓ Alveolar ventilation formula = (tidal volume dead space) x respiratory rate---putting value 500-150ml x 12 breath/min= 4200ml/min

#### Apparatus dead space:

- ✓ When using mask or anesthetic circuit tubing or ETT and ventilator tubing.
- ✓ This added to the conducting zone

#### Factor affecting dead space

- The Apex of the healthy lung is the largest contributor of functional dead space
- Pattern of breathing has no effect on Dead space, but if asked choose shallow breathing
- Size of the object: increase with body size
- Age: an infancy anatomical dead space is higher for body weight
- Posture: sitting 147ml, supine 101ml
- Drugs: Bronchodilator will increase dead space
- The Low cardiac output increase the alveolar dead space (increasing west's zone 1)

Increase dead space	Decrease dead space
<ul> <li>COPD, asthma</li> <li>ETT</li> <li>Increase the size of individuals</li> <li>Zone 1</li> </ul>	<ul> <li>Tracheostomy</li> <li>Bronchoconstriction</li> <li>Supine position</li> <li>Atelectasis</li> <li>A Decrease in diameter of the airway</li> </ul>

#### Intra-pleural Pressure

- ❖ Intrapleural pressure (also called intrathoracic pressure) refers to the pressure within the pleural cavity. Normally, the pressure within the pleural cavity is slightly less than the atmospheric pressure, in what is known as negative pressure.
- Causes of negativity of intrapleural pressure:
  - ✓ The Lymphatic system drains the pleural fluid, generating a negative intra-pleural pressure. (-2 mm Hg)
- \* Measurement of intra-pleural pressure: can be measured directly by introducing a needle to the pleural cavity or by the indirect method by introducing the esophageal balloon into esophagus
- Significance of intra-plural pressure:
  - Prevent the collapsing tendency of lungs
  - Increases the venous return
- Atmospheric pressure:
  - The pressure of the air around us. At sea level the atmospheric pressure is 760 mm Hg, at higher altitude, the pressure is lower
- intra-pulmonary pressure:
  - ✓ The pressure within the bronchial tree and alveoli. The pressure fluctuates below and above atmospheric pressure during each cycle of breathing
- Important Points and Concept:
  - ✓ Intra- plural pressure: It represents the pressure in the thin film of fluid between the lung and chest wall
  - Subatmospheric pressure (-) act as a force to prevent collapse the lung
  - During normal restful breathing, intrapleural pressure is always subatmospheric (or negative) and thus act as a force to expand the lung
  - At the end of expiration, intrapleural pressure is subatmospheric
  - During inspiration intrapulmonary pressure drops below atmospheric pressure (-1 mm Hg). Airflows into the lungs, down the pressure gradient, until intrapleural pressure = atmospheric pressure
  - During expiration, intra-pulmonary pressure rises above atmospheric pressure (+1 mm Hg). Gases flow out of the lungs, down the pressure gradient, until intra-pulmonary
  - Lung collapse is prevented by: adhesion of the pleural membrane
  - During spontaneous ventilation, the body maintains a residual its lungs to prevent them from collapse. volume in

#### Chapter 3

The Lungs

#### Naseem Sherzad High-Yield Points

- Difference between systemic and pulmonary circulation---------Low resistance in the pulmonary circulation
- Venous and arterial PO2 and PCO2----same on the dorsum of the warm hand
- \* Bronchial spasm physiologically present at early morning. Symptoms of asthma are usually worse at night and in the early morning or in response to exercise or cold air
- The umbilical vein of the fetus like the pulmonary vein of the adults carries the circulation most highly oxygenated blood
- \* Fraction of inspired oxygen (FiO2) maximum dose, which does not cause fetolental adrenoplasia is 0.65 and this is also the safest dose in the pregnant lady
- For any given level of exercise, oxygen consumption is higher in pregnant than in non-pregnant women
- ❖ O₂ debt:
  - ✓ Oxygen debt is the amount of extra oxygen that must be taken after exercise to restore the muscles to the resting condition
  - ✓ When a person stop exercising, the rate of oxygen uptake does not immediately return to pre-exercise level, it returns slowly
  - ✓ This extra oxygen is used to repay the oxygen debt incurred during exercise
  - ✓ The early portion of oxygen debt is called alactacid oxygen debt and amount to about 3.5 liters. The latter portion is called the lactic acid oxygen debt and amount to about 8 liter

#### **Pulmonary Artery**

- It Supplies alveoli
- Highest blood velocity, the highest content of CO2
- Contain Highest mixed venous blood
- ❖ O₂ dependent K<sup>+</sup> channel are present in the pulmonary artery
- The Pulmonary artery pressure increase in hypoxia because hypoxia cause vasoconstriction
- Pulmonary vasoconstriction occurs due to reduced systemic (arterial) PO2
- Saddle embolus cause sudden death by blocking pulmonary arteries

#### Diffusion and perfusion limited Gases

- Highest diffusion affinity-----CO
- ❖ Diffusion Limited Gases-----O₂-during exercise, fibrosis, emphysema and CO.
- ❖ Perfusion Limited Gases---- CO₂, N₂O and O₂ (under normal condition)
- ❖ Solubility coefficient of CO₂ is 0.57 and that of O₂ is 0.024
- ❖ CO₂ diffuse 22 times faster than O₂ into the blood
- \* The highest diffusion capacity across respiratory membrane and body fluid--CO2
- Anemia-----PaO2 + SaO2----normal
- Meth Hb+ CO poisoning:
  - ✓ PaO₂----Normal
  - ✓ SaO₂------Decreased

## O2 level Differences

- . Highest PO2 in pulmonary capillaries and lowest in the umbilical artery
- . Highest venous O<sub>2</sub> saturation in the renal vein
- ❖ Highest O₂ tension present in pulmonary capillaries
- Less in the fetus than mother: PCO2
- Oxygen is taken up to lung through simple diffusion
- ♣ Lowest O₂ level In SVC
- ❖ PO₂ at sea level in normal adult---97%
- . Lowest capillary permeability in ----- Brain
- Glomerular capillary has the highest pressure because of----short afferent arteriole
- Reduction in blood supply to brain cause——seizure
- HCO<sub>3</sub> that rises with 10mm Hg of PCO<sub>2</sub> is 3
- The most common cause of cell injury worldwide is hypoxia
- Oxygen level in the blood will decrease in hypoxic hypoxia
- \* Alveolar ventilation is 4.2 L/min

#### **Carbon Monoxide Poisoning**

- It is a colorless and odorless gas
- Hb has 250 times more affinity to bind with CO as compared to O2
- Carbon monoxide Hb, shifts the oxy-Hb curve to left
- It also inhibits Cytochrome
- Arterial PaO<sub>2</sub> is normal
- When there is 70% carbon monoxide Hb in blood, death occurs



#### **Important Devices**

#### Capnometer:

 A Monitoring device that measures and numerically displays the concentration of carbon dioxide in exhaled air

#### \* Radford nomogram:

 It is used to predicate necessary tidal volume for artificial respiration on the basis of respiratory rate, body weight and sex

#### \* Spirometry:

- Most volumes and capacities can be measured by using a spirometer, but the residual volume and any capacity containing residual volume cannot be measured with a
- TLC and FRC and RV can't be measured using simple Spirometry

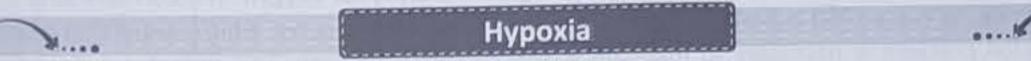
Chapter 3

The Lungs

## Factors affecting Gas Diffusion Through Respiratory Membrane

#### ....

- The Thickness of respiratory membrane------Inversely proportional
- The Surface area of respiratory membrane-----Directly proportional
- Diffusion co-efficient of gas ------Directly proportional
- Diffusion co-efficient----Ratio of solubility of co-efficient of a gas to under root of its mole.



#### 1) Hypoxic hypoxia:

- Occur when not enough oxygen is in the air, O2 content and saturation is decreased
- Most common in high altitude
- 2) Stagnant hypoxia:
  - Blood flow to the tissue is slow, despite normal Hb and PO2
  - Causes: Polycythemia, hypotension, heart failure
- 3) Histotoxic hypoxia:
  - Tissue is <u>unable to use oxygen</u> due to inhibition of enzyme responsible for internal respiration
  - Cyanide poisoning: inhibition of Cytochrome oxidase, the most common cause
  - Alcohol and barbiturate which prevent dehydrogenase
- 4) Anemic hypoxia:
  - The arterial PO2 is normal but the amount of Hb available to carry O2 is reduced
  - · Occur in Meth-Hb
- 5) Hypoxemia:
  - Hypoxemia is defined as a decrease in the partial pressure of oxygen in the arterial blood
     when the partial pressure of oxygen is less than 60 mm Hg, when hemoglobin oxygen
     saturation is less than 90%
  - V/Q mismatch is the most common cause of hypoxemia

#### **Chest Pain**

- . Chest pain related with respiration------Costochondritis
- Chest pain related with changing position------Pericarditis

# Hb—O<sub>2</sub> Dissociation Curve



- The O2---Hb dissociation curve is Sigmoid shape
- The term "affinity" is used to describe oxygen attraction (love) to hemoglobin binding sites, Higher the affinity, higher will be the attraction (love) of oxygen to hemoglobin binding sites
- Shift to Left-----Releases Less to the tissue, more love of Hb and O2 (higher affinity) and will not release to tissue--- Easier to load O2 but difficult to unload it.
- Shift to Right-----Release more to the tissue, Hb and O2 not loving (low affinity) and will release it to the tissue. Difficult to load O2 but easier to unload the O2
- P50 or T50 is a conventional measure of hemoglobin affinity for oxygen. The normal P50 is 26.7 mm Hg. Increased P50 indicates a rightward shift of the standard curve, which means that a larger partial pressure is necessary to maintain a 50% oxygen saturation. This indicates a decreased affinity. Conversely, a lower P50 indicates leftward shift and a higher affinity
- Haldane effects: increase in CO2 in blood will cause O2 to be displaced from Hb and binding of O2 with Hb displace CO2 from the blood. This called Haldane effects. The Haldane effects describe how oxygen concentration determine hemoglobin's affinity for carbon dioxide
  - ✓ H------Hemoglobin
  - ✓ A-----Affinity
  - ✓ IDane-----Carbon dioxide
- Bohr effects: The Bohr effects describes how carbon dioxide and H\* affect hemoglobin's affinity for oxygen
  - -----Bohr effect
  - -----Oxygen
  - -----Hydrogen
  - -Released in tissue

|--|

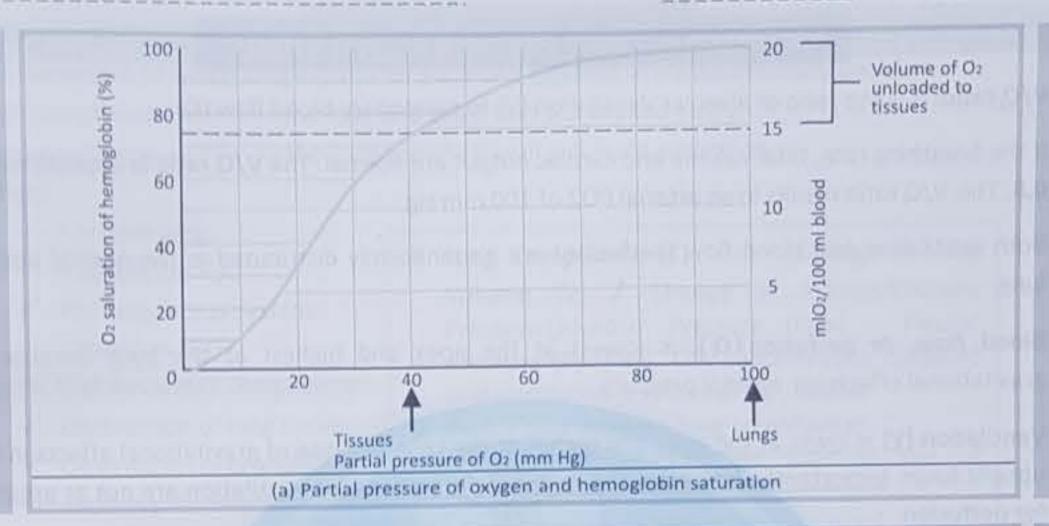
- Low temperature
- Low H+ (Alkalosis) inc. Ph
- Low PCO2
- Low 2,3-DPG
- HbF---fetal Hb (extreme left shift)
- Co-poisoning
- Increase affinity of hemoglobin
- The HaLdane shift is the leftward shift of the oxygen dissociation curve, which signifies an increased affinity of Hb for CO2. At low pO2 levels, the carrying capacity of CO2 increases. in other words, there is an increased affinity for CO2 when there is less O2 bound to hemoglobin

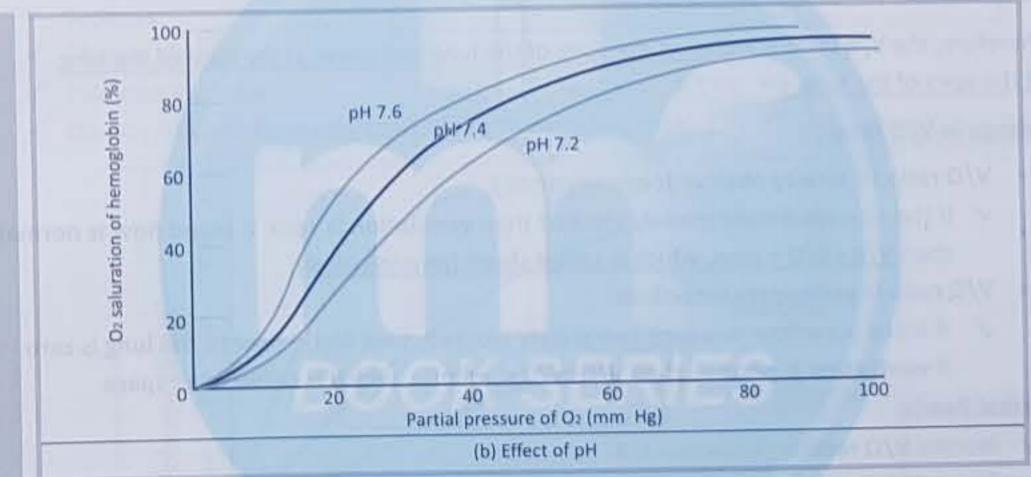
# Shift to right

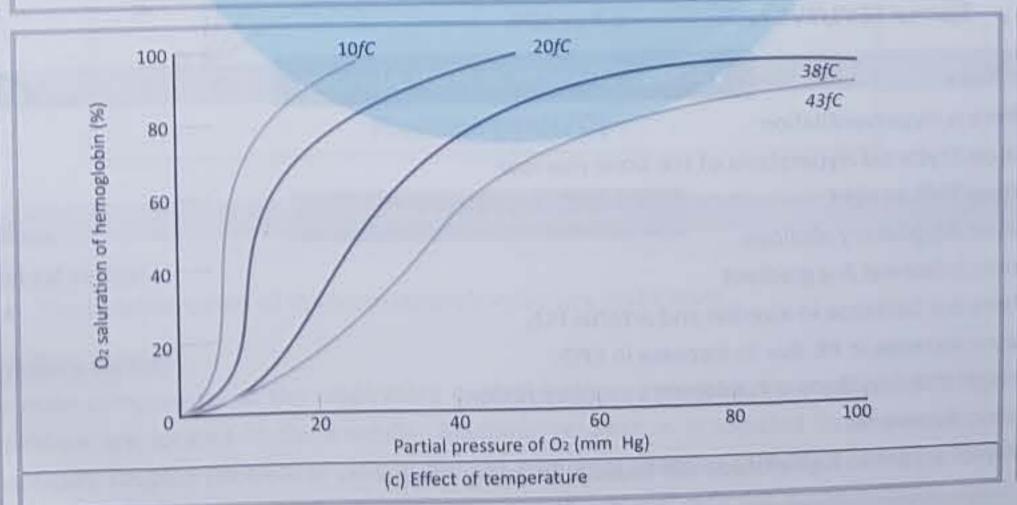
- temperature (blood warmed before transfusion will cause the shift to right)
- High H+ (acidosis), dec. Ph
- High PCO<sub>2</sub>
- High 2,3-DPG:
  - ✓ Increase by thyroxin
- High altitude
- Exercise
- Taut Hb,
- Chronic iron deficiency anemia
- The Rightward shift of the oxygen dissociation curve is the  $Boh\underline{R}$  shifts which signify decreased affinity of Hb for O2

Chapter 3

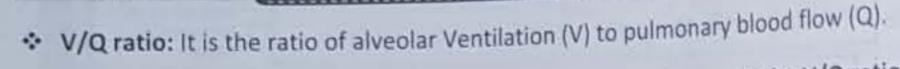
The Lungs







Ventilation Perfusion Mismatch or "V/Q Defects"



- If the breathing rate, tidal volume and cardiac output are normal. The V/Q ratio is approximately 0.8. This V/Q ratio results in an arterial PO2 of 100 mm Hg
- . Both ventilation and blood flow (perfusion) are nonuniformly distributed in the normal upright lung.
- \* Blood flow, or perfusion (Q), is lowest at the apex and highest at the base because of gravitational effects on arterial pressure
- . Ventilation (V) is lower at the apex and higher at the base because of gravitational effects in the upright lungs. Importantly, however, the regional differences for ventilation are not as great as for perfusion
- \* Therefore, the V/q ratio is higher at the apex of the lung and lower at the base of the lung
- At the apex of the lung pH is >7.4
- Change in V/Q ratio:
  - V/Q ratio in airway obstruction:
    - ✓ If the airways are completely blocked then ventilation is zero. If blood flow is normal, then V/q = 0/Q = zero, which is called shunt (physiological).
  - V/Q ratio in pulmonary embolism:
    - If blood blow flow to a lung completely blocked, then blood flow to the lung is zero. If ventilation is normal, then V/Q=V/0 = infinite, which is called dead space
- Clinical Pearls:
  - ✓ Normal V/Q ratio is—
  - ✓ Normal FEV1/FVC ratio———0.8 or 80%

# Various Changes at High Altitude

- There is Hyperventilation
- Cause Erythroid Hyperplasia of the bone marrow
- Cause Shift to right -----increase 2-3 DPG concentration
- Cause Respiratory alkalosis
- There is Normal A-a gradient
- There is a Decrease in alveolar and arterial PO2
- Cause Increase in Hb due to increase in EPO
- In high attitude, there is Pulmonary vasoconstriction
- Cause Hypoxemia
- "Rapid" ascent to high altitude will cause pulmonary edema

# Chapter 3

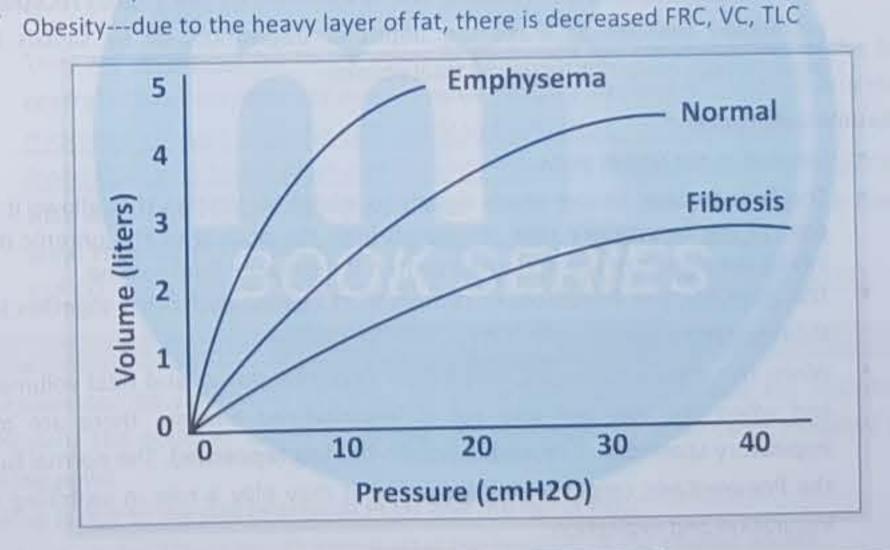
#### **Lung Compliance**



The Lungs

- It is the extent to which lung expand for each unit increase in transpulmonary pressure
- Low compliance----the lung and chest wall will resist expansion
- Value:
  - ✓ For both lung: = 200ml/cm H<sub>2</sub>O
  - ✓ For lung-thorax system: 110ml/cm H<sub>2</sub>O
- Factor that decreases compliance:
  - ✓ Obstruction of lung tissue
  - Obstruction of bronchioles
  - Kyphosis
  - Scoliosis
  - Fibrotic pleurisy
  - ✓ Pulmonary edema

- Lung Compliance (C) = Change in Lung Volume (V) / Change in Transpulmonary Pressure (Alveolar Pressure (Palv) - Pleural Pressure (Ppl)} e.g. CO2 concentration constant and ventilation is reduced= CO2 double
- Factor that increase lung compliance:
  - Physiological: Old age (due to loss of elasticity)
  - Pathological: emphysema (smoker)



# **Control of Respiration**

- in Cerebral cortex
  - The cerebral cortex of the brain controls voluntary respiration
- in Medullary center:

The main components of the respiratory control pattern generator responsible for automatic respiration are located in the medulla. Rhythmic respiration is initiated by a small group of synaptically coupled pacemaker cells in the pre-Bötzinger complex (pre-BÖTC) on either side of the medulla between the nucleus ambiguous and the lateral reticular nucleus. These neurons

discharge rhythmically, and they produce rhythmic discharges in phrenic motor neurons that are abolished by sections between the pre-Bötzinger complex and these motor neurons. They also contact the hypoglossal nuclei, and the tongue is involved in the regulation of airway resistance.

## Dorsal respiratory groups

- Responsible for inspiration
- The dorsal respiratory group is involved in the generation of the respiratory rhythm, and is primarily responsible for the generation of inhalation. It is also stimulated via the apneustic center in the lower pons

#### Ventral respiratory groups

- Responsible for expiration
- Inactive during normal quiet respiration

### Pontine center

#### Apneustic center

- Located in the lower pons
- The apneustic center sends signals for inspiration for long and deep breaths. It controls the intensity of breathing and is inhibited by the stretch receptors of the pulmonary muscles at maximum depth of inspiration, or by signals from the pnuemotaxic center. It increases tidal volume.

#### Pneumotaxic center

- Located in the upper pons
- The Pneumotaxic center sends signals to inhibit inspiration that allows it to finally control the respiratory rate. Its signals limit the activity of the phrenic nerve and inhibit the signals of the apneustic center. It decreases tidal volume.
- The apneustic and Pneumotaxic centers work against each other together to control the respiratory rate.
- When this area is damaged, respiration becomes slower and tidal volume greater, and when the vagi are also cut in anesthetized animals, there are prolonged inspiratory spasms that resemble breath-holding (apneusis). The normal function of the Pneumotaxic center is unknown, but it may play a role in switching between inspiration and expiration.

# Effect of Transaction at various level

- . Injury Above pons---regular breathing
- Injury Below medulla—<u>respiration stop</u> (phrenic nerve cut )
- ❖ Injury Below Pneumotaxic center: <u>sustained inspiration apneusis</u> with the vagal cut. However, if the vagus is intact, respiration is continuous
- ❖ Injury Below apneustic center: gasping type irregular respiration continues, with

Chapter 3

# The Lungs

# Chemoreceptors

Peripheral chemoreceptors (carotid--most important and aortic bodies) and central chemoreceptors (Medullary neurons) primarily function to regulate the respiratory activity. This is an important mechanism for maintaining arterial blood PO2, PCO2, and pH within appropriate physiological ranges.

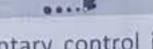
## Peripheral chemoreceptor:

- They are very sensitive to reduction in the partial pressure of oxygen less than 60 mm Hg
- Low PO<sub>2</sub> stimulate respiratory center through stimulation of peripheral chemoreceptors
- Most sensitive: decrease arterial PO2
- Less sensitive to: decrease Systemic Arterial pH (↑H+ ion concentration)/increase arterial of PCO<sub>2</sub>

### Central Chemoreceptor:

- The chemoreceptor presents in the brain are called central chemoreceptors
- They are situated in the deeper part of the medulla oblongata, close to the dorsal group of neurons. This area is known as chemosensitive area and neuron are called chemoreceptors
- They are very sensitive to increases in hydrogen ion concentration in the brain ECF, so central chemoreceptors are most sensitive to CO2-induced H<sup>+</sup> production in the Brain ECF
- Hydrogen ion cant cross the BBB and blood cerebrospinal fluid barrier
- Blood CO2 cross blood-brain and blood-CSF barrier. CO2 combines with H2O to form H2CO3 that dissociates into HCO3- ions and H<sup>+</sup> ions. This H<sup>+</sup> ion stimulates the chemosensitive area. Thus blood CO2 can affect the chemosensitive area
- CSF CO<sub>2</sub> has a more potent effect on the chemosensitive area than blood CO<sub>2</sub>

# **Breath Holding**



- Respiration can be voluntarily inhibited for some time, but eventually the voluntary control is overridden. The point at which breathing can no longer be voluntarily inhibited is called the breaking point.
- ❖ Breaking is due to the rise in arterial PCO₂ and the fall in PO₂.
- Individuals can hold their breath longer after the removal of the carotid bodies.
- \* Breathing 100% oxygen before breath-holding raises alveolar PO2 initially, so that the breaking point is delayed. The same is true of hyperventilating room air, because CO2 is blown off and arterial PCO2 is lower at the start.
- Reflex or mechanical factors appear to influence the breaking point, since subjects who hold their breath as long as possible and then breathe a gas mixture low in O2 and high in CO2 can hold their breath for an additional 20 sec or more.
- Psychological factors also play a role, and subjects can hold their breath longer when they are told their performance is very good than when they are not.

A ....

# PATHOLOGY

Table with some	high yield points
Disease	High yield

Disease	High yield
Chronic Bronchitis  (Definition based on clinical feature)	Blue bloater
> Emphysema (Morphologic definition)	<ul> <li>Pink puffer and Barrel chest</li> <li>The TLC, RV and FRC increased but the</li> <li>VC is decreased in emphysema</li> </ul>
> Silicosis	Egg-shell calcification
> Bronchial asthma	Curschmann's spiral     Charcoal Leyden crystals
<ul> <li>Kartagener's syndrome         (Autosomal recessive disorder)         Caused by multiple mutation that encode for the dynein gene         Absent or irregular dynein arm of cilia     </li> </ul>	<ul> <li>Bronchiectasis</li> <li>Sinusitis,</li> <li>Infertility</li> <li>Situs inverses(transposition of viscera)</li> </ul>
Asbestosis	<ul> <li>Ferruginous bodies</li> <li>"Ivory white" calcified.</li> </ul>
> Sarcoidosis	<ul> <li>Non-caseating granuloma on biopsy</li> <li>Schaumann bodies (laminated calcification), Hypercalcemia</li> <li>Asteroid bodies (satellite giant cell cytoplasmic inclusion)</li> </ul>
> Interstitial fibrosis	* Honey-comb appearance on X-ray

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The Lungs

# **Respiratory Failure**

Hypoxia Normal or low PaCO2		Type-II Respi	ratory Failure
		Hypoxia Raised PaCO2	
Acute	Chronic	Acute	Chronic
<ul> <li>ARDS</li> <li>Pneumonia</li> <li>Pulmonary edema</li> <li>Pulmonary embolism</li> <li>Pneumothorax</li> </ul>	<ul> <li>Emphysema</li> <li>Lung fibrosis</li> <li>Right to left shunt</li> </ul>	<ul> <li>Acute severe         asthma</li> <li>Acute         exacerbation         of asthma</li> <li>Upper airway         obstruction</li> <li>Narcotic drugs</li> </ul>	<ul> <li>COPD</li> <li>Sleep apnea</li> <li>Polio</li> <li>Ankylosing spondylitis</li> <li>Myopathy</li> </ul>

# Difference between obstructive and restrictive lungs disease

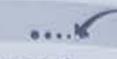
Obstructive disease	Restrictive disease	
Characterized by reduction airflow	<ul> <li>Characterized by reduction airflow, reduced expansion of lung</li> </ul>	
Low FEV1/Vc, less than 0.8 or 80%	<ul> <li>Both FEV1 and FVC are low</li> <li>That's why FEV1/FVC ratio is normal</li> <li>Decreased TLC and FVC</li> </ul>	
■ Example  ✓ COPD  ✓ Asthma  ✓ Bronchiectasis	■ Example  ✓ Interstitial lung disease  ✓ Scoliosis  ✓ Neuromuscular causes  ✓ Marked obesity	

# Sarcoidosis

- 2 .... The diagnostic Histopathologic feature of Sarcoidosis is the non-caseating epithelioid granuloma, irrespective of the organ involved.
- Asteroid bodies, stellate inclusions enclosed within giant cells. Their presence is not required for the diagnosis of Sarcoidosis. They may also occur in granuloma of other origins.
- Bilateral Hilar lymphadenopathy
- Skin is the most common extra-pulmonary presentation, means second most commonly affected organ after the lungs. The most common lesion is erythema nodosum. Erythema nodosum is more common in women and northern European and is associated with a favorable overall prognosis
- Can cause heart block, splenomegaly and renal stone
- Diagnosis:
  - ✓ Elevated serum ACE
  - √ Hypercalcemia,
  - ✓ Lymphopenia

# The Lungs

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Pulmonary Embolism (PE)

- Definition: the blockage of pulmonary arteries by thrombus, fat or air emboli and tumor tissue V/Q is infinite, which is called dead space—V/0= everything divide by zero give infinite-----
- here ventilation (V)= normal but perfusion (Q) = is zero so V/0= infinite
- The Most common factor in the pathogenesis of thrombus is the endothelial injury

## Causes of Thromboembolism:

- ✓ Prolonged immobilization—Most common cause
- ✓ OCP
- ✓ Amount of air required to cause pulmonary embolism is 100cc

#### A Clinical features:

- ✓ Most common symptoms of PE is respiratory distress (dyspnea)— 75-85%
- ✓ Pulmonary embolism causes respiratory alkalosis
- ✓ Most pulmonary emboli (60% to 80%) are clinically silent because they are small
- ✓ In pulmonary artery embolism the alveolar PAO₂ increase (150 mm Hg) and PACO2 decrease (0 mm Hg)....BRS Physiology page 135 table

### in Investigation:

- Best investigation/gold standard for pulmonary embolism is CT pulmonary angiography(CT-PA), V/Q scan is choice in pregnancy
- ✓ Most common finding on ECG——sinus tachycardia

### " Complication:

Life-threatening complication following fracture is pulmonary embolism

# Naseem Sherzad High-Yield Points

- The commonest site of highest airway resistance—Medium-size bronchi
- · Commonly affected in asthma--- Medium-size bronchi
- · Commonly affected in PE---Medium-size vessels
- · Commonly affected in pulmonary infarction--Small-size vessel
- · Alpha-1 anti-trypsin deficiency effect---Alveolar duct and alveoli
- . The Most common cause of pulmonary embolism is DVT
- . The Most common source for pulmonary embolism is femoral vein
- . Most common site of DVT is the popliteal vein
- Duplex ultrasound is the diagnostic modality of choice for detection of infrainguinal DVT

# Classification of Lung Tumors

- i. Small cell lung cancer (SCLC) —15%—Arises from neuroendocrine (Kulchitsky) cells.
- a) Adenocarcinoma ---40%
  - · Morphology:
    - ✓ Peripheral gray-white mass with pleural puckering
    - ✓ Develop in area of parenchymal scarring

# Chapter 3

The Lungs

- ✓ The highest frequency of K-RAS mutations
- ✓ About 80 % contain mucin
- b) Squamous cell carcinoma ----30%
  - · Morphology:
    - ✓ Gray white infiltrating tumor
    - Highest frequency of p53 mutation of all histological type
    - Keratinization (Keratin pearls)
    - Intercellular bridges
    - Fungiform growth
    - ✓ Mitotic activity is higher in poorly differentiated tumor
- Large cell carcinoma --- 10%--- poor prognosis



# **Paraneoplastic Syndrome**

# Adenocarcinoma: 38 %

- Thrombophlebitis
- Non-bacterial verrucous Endocarditis

## Squamous cell cancer: 20 %

- Hypercalcemia (PTH-related peptide)
- Small cell cancer: 14 %
  - Cushing syndrome(ACTH)
  - Syndrome of inappropriate ADH secretion (SIADH) (imp)
  - Lambert-Eaten syndrome
  - Small cell carcinoma are treated primarily with chemotherapy and radiation

# Large cell carcinoma: 3 %

- Gynecomastia (Gonadotrophin)
- . Renal cell carcinoma can produce many Paraneoplastic syndromes like producing erythropoietin, PTH-related Peptide, Renin and Gonadotrophin that cause systemic effects.



# **Emphysema**



- It is characterized by permanent enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls without obvious fibrosis.
- There is respiratory acidosis and an increase in lung compliance in emphysema

# Emphysema is classified into four major types

# i. Centriacinar emphysema:

- In this type of emphysema, the central or proximal parts of the acini, formed by respiratory bronchioles, are affected, whereas distal alveoli are spared.
- It is the most common type.
- It is strongly associated with smoking. Most severe in the upper lobe.

# ii. Panacinar emphysema:

In this type, the acini are uniformly enlarged from the level of the respiratory bronchiole

to the terminal blind alveoli.

Associated with alpha1-antitrypsin deficiency

# iii. Paraseptal emphysema:

- Dilation involves mainly the distal part of the Acinus, including the alveoli and to a lesser
- extent the alveolar duct.
- It is associated with large subpleural bullae, or bleb, which can predispose to

# iv. Irregular emphysema:

Pneumothorax

Irregular involvement of the Acinus with scaring within the walls of enlarged air spaces

## Pathogenesis

- The Imbalance between protease and anti-protease:
  - Alpha-1 antitrypsin deficiency: protease can't be inhibited because of genetic deficiency of anti-protease i.e. AAT
- The Imbalance between oxidant and anti-oxidant:
  - Anti-oxidant is depleted by the reactive oxygen species of tobacco, which result in tissue damage and "Function" inactivation of alpha-1 antitrypsin.

# **Naseem Sherzad High-Yield Points**

- Protease: This is produced by neutrophil and macrophage, which is dangerous because it causes damage to the air space.
- Anti-protease: it best for the body because it causes lysis of protease and thus prevents the destructive feature of protease
- PiM allele is normal, PiZ is the most common relevant mutation.

# Difference between Asthma and COPD

#### Asthma

# Chronic Obstructive Pulmonary Disease (COPDS)

- The Investigation of choice for asthma is PFTS (FEV1 diagnostic). Remember eosinophilia is non-specific test because it also occurs in other conditions like a parasitic infection.
- The most common risk factors for developing asthma is having a parent with asthma
- Methacholine challenge differentiate between asthma and COPD
- Asthma is a chronic inflammatory Reversible disorder.
- The most permanent cell on the peripheral smear is eosinophils

- Cause irreversible obstruction of airflow for
- which smoking is the most important risk factor
- This is the most common cause of Corpulmonale
- Two commonly used anticholinergics in patients with COPD include ipratropium bromide and tiotropium bromide
- Risk factors:
  - Smoking—most important risk factor
  - Alpha-1 antitrypsin deficiency
  - o Occupations (coal miners, cadmium exposures)
  - o Chronic asthma
  - o Cannabis smoking

Chapter 3

The Lungs

# **Cystic Fibrosis**

- Autosomal recessive defect in CFTR gene on chromosome 7, commonly deletion of Phe 508
- Mutation often causes abnormal protein folding, resulting in degradation of the channel before reaching the cell surface
- This is the Most common cause of bronchiectasis
- CFTR channel actively secretes Cl' in the lung and Gl tract and actively reabsorb Cl' from sweat
- It mainly affects the lungs and digestive system

#### Clinical features:

- Salty tasting skin, the mother may notice that the child is salty when kissed
- Poor weight gain Inspite of excessive appetite
- Persistent coughing and shortness of breath
- Obstruction in the pancreas can lead to malnutrition and poor growth. It has also been associated with an increased risk of diabetes and osteoporosis.
- Male can be infertile due to absence of the Vas deferens

## investigation

- There is an increase in sodium chloride content in the sweat (sweat chloride elevated to over 80 mEq/L). Increased concentration of Chloride ion in the sweat test is diagnostic There is also increased concentration of chloride in saliva
- Treatment: N-acetylcysteine to loosen mucus plug

# Pulmonary function tests (PFTs)



- . Definition: Pulmonary function tests are non-invasive tests that show how well the lungs are working.
- PFT Measures:
  - Tidal volume
  - Vital capacity
  - · Function residual capacity (FRC): This is the amount of air left in the lungs after exhaling normally.
  - Residual volume: This the amount of air left in the lungs after exhaling as much as you can.
  - Total lung capacity
  - \* Forced vital capacity (FVC): this is the amount of total volume exhaled forcefully and quickly after inhaling as much as you can
  - Forced expiratory volume (FEV1)\*: The volume exhaled in the first second
  - · Forced expiratory flow
  - · Peak expiratory flow rate

# PFT can be done with two methods:

- Spirometry
- If Spirometry not available, a peak flow meter may be used

# HIGH YIELD POINTS

- 1) The most common cancer in the male is prostatic carcinoma.
- The most common cancer in the female is breast carcinoma.
- 3) The most common cancer leading to death in both men and women is lung carcinoma.
- 4) The most aggressive, a highly malignant and metastatic lung carcinoma is small cell carcinoma
  - and the most common carcinoma of the lung is Adenocarcinoma.
- 5) Squamous cell carcinoma shows the highest number of P53 mutations of all Histologic types of lung carcinoma.
- 6) Bronchogenic carcinoma is the most common cause of superior vena cava syndrome.
- 7) Risk factors for Bronchogenic carcinoma are smoking, radon, and asbestosis. It is important to note, that people who are exposed to asbestosis are more likely to develop Bronchogenic carcinoma more than to develop mesothelioma.
- Bronchial carcinoma clinical presentation (IMP for MCQs): Hoarseness in bronchial carcinoma is due to recurrent laryngeal nerve palsy, dysphagia in bronchial carcinoma is due to esophageal invasion.
- Bronchogenic carcinoma which is strongly related to smoking and arises centrally
  - Squamous cell carcinoma
  - 5mall cell carcinoma
  - \* Note: Bronchogenic carcinoma which having "S" in the beginning tell us about two things
    - That it is strongly related to smoking and
    - Its Arises centrally like the above small cell and Squamous cell carcinoma
- 10) Pulmonary Hemartoma is the most common benign tumor of the lung.
- 11) Pleural plaques are the characteristic feature of mesothelioma.
- 12) Bronchiectasis: Cystic fibrosis is the most common congenital cause of bronchiectasis in US and Tuberculosis is the most common acquired cause of bronchiectasis worldwide.
- 13) Emphysema cause an increase in compliance and cause respiratory acidosis
- 14) Centriacinar is the most common type of emphysema, which affects the upper lobes.
- 15) TB of the vertebral body is called Potts disease.
- 16) Cavitation is the characteristic of secondary but not of primary tuberculosis.
- 17) In pneumoconiosis the differentiating lesion is fibrosis
- 18) Caplan syndrome: it is a combination of rheumatoid arthritis (RA) and pneumoconiosis that manifests as intrapulmonary nodules, which appear homogenous and well defined on chest X-ray
- 19) The most common cause of respiratory distress in pre-term neonate is hyaline membrane disease
- 20) The most common cause of respiratory distress in term or post-term neonate is meconium
- 21) Mendelson's syndrome: is a chemical or aspiration pneumonitis caused by aspiration during anesthesia, it is acute lung injury after the inhalation of regurgitated gastric contents and
- 22) Most common cause of Bronchitis--------Respiratory syncytial virus

Chapter 3

The Lungs

# **Occupational Lung Disease**

# Silicosis

- ✓ Silicotuberculosis
- ✓ Snowstorm appearance
- ✓ Egg shell calcification
- ✓ Effect upper zone of lung

#### Occupations:

- ✓ Sand blasting
- Metal grinding
- Boiler scaling
- Pottery and ceramic industry
- Gold industry
- Rock mining
- Iron and steel industry

#### Mnemonic

Asbestosis is in the roof and affects the floor (base of lung), silica and coal are from the earth and effects the roof (upper lobe)

#### **Asbestosis**

- Bronchogenic CA > Mesothelioma
- Ground glass appearance
- Finger clubbing
- ✓ Cyanosis and cardiac distress
- ✓ Lower two-third of lung
- ✓ Pleural calcification occurs in about 50% with asbestosis related disease, especially diaphragmatic pleura

#### Occupations:

- √ Fireproof textile
- ✓ Roof tiling
- ✓ Engine Gaskets
- ✓ Fireproof blanket and suits
- ✓ Shipbuilding industry
- Brake tiling

# Byssinosis

- Caused by inhalation of cotton dust (textile and fiber industries)
- smoking significantly exacerbate Byssinosis

# **Handy Points**

- Iron laden mitochondria seen in Sideroblastic anemia
- Subpleural collection of <u>carbon-laden macrophage</u> is seen in Anthracosis
- Sidrophages, which is <u>Hemosiderin containing Macrophage</u>.
- Bagassosis: From Sugar dust
- Berylliosis: from Beryllium
- Anthracosis: From coal worker

# **Hypersensitivity Pneumonitis**

- · Hypersensitivity pneumonitis which is also known "extrinsic allergic alveolitis" result from inhalation of a wide variety of Organic antigens like farmer lung which result from Mouldy hay, Bird fanciers lung which result from avian execrate, proteins and feather etc.
- Farmer are most likely exposed to grain dust

Cardiovascular System

# CHAPTER

# CARDIOVASCULAR SYSTEM

"Only from the Heart can you touch the sky" -- Rumi

# ANATOMY

Heart

## 1) Layers of heart:

- Epicardium
  - ✓ It is the Outer visceral layer
  - ✓ It is Supplied by Epicardial coronary artery
  - This is actually the visceral layer of the pericardium
- Myocardium
  - ✓ It is the Middle thick layer, cardiac muscle found in the myocardium of the heart
  - The SA node is located in the myocardium of the right atrium just deep to Epicardium
- Endocardium:
  - ✓ It is the Inner thin layer
  - ✓ Sub-Endocardium—Contain conduction system of the heart
  - Sub-endocardial region, Most vulnerable to ischemia so most common site of MI, as this part receives almost no blood supply during systole

#### 2) Pericardium:

- Fibrous pericardium:
  - ✓ The fibrous pericardium is attached to the sternum by sternopericardial ligament.
- Serous pericardium:
  - ✓ Parietal layer
    - o Supplied by Phrenic nerve which runs In close association with Pericardiophernic vessels
    - Pain sensitive
    - o For this reason, 'pain' related to a pericardial problem may be referred to the supraclavicular region of the shoulder.
  - ✓ Visceral layer
    - O Visceral layer of the serous pericardium is also called Epicardium
- · Pericardial cavity:
  - The pericardial cavity is the potential space formed between the two layers of
  - Between Parietal layer and visceral layer (also called Epicardium)

Margins of Heart

- \* The of Apex of heart is formed by-----Left ventricle
- \* Base or posterior part of heart formed by------Left atrium
- The Right border of the heart is formed by-----Right atrium
- On X-Ray right border of the heart is formed by-----SVC
- Greatest sternocostal projection -------Right vertical
- A stab above xiphisternal joint at 6th costal cartilage just right will damage---right atrium
- For radiologic evaluations, a thorough understanding of the structures defining the cardiac borders is critical.
  - The right border in a standard posterior-anterior view consists of the superior vena cava, the right atrium, and the inferior vena cava.
  - The left border in a similar view consists of the arch of the aorta, the pulmonary artery, and the left ventricle.
  - The inferior border in this radiologic study consists of the right ventricle and the left ventricle at the apex.
  - In lateral views, the right ventricle is seen anteriorly, and the left atrium is visualized posteriorly.

# The Apex of heart:

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- Formed by the left ventricle
- Directed downward, forwards and to the left
- Lies posterior to the left 5th intercostal space in adult, usually 8 to 9cm from the midsternal line or 1.5cm medial to the mid-clavicular line
- Maximal pulsation of the heart (apex beat) heard here
- Blood supply: LAD >> Right Marginal artery

# **Cardiac Plexus**

\* Branches from both the parasympathetic and sympathetic systems contribute to the formation of the cardiac plexus.

# Cardiac plexus comprises two parts, a superficial and deep part

- The superficial part of the cardiac plexus lies in the concavity of the aortic arch in front of the ligamentum arteriousm
  - ✓ Sympathetic: Superior cervical cardiac branch of the left sympathetic chain
  - ✓ Parasympathetic: Left vagus nerve
- The deep part of the cardiac plexus is larger than superficial and lies behind the aortic arch in front of the bifurcation of the trachea.
  - ✓ It is formed by the cardiac nerves derived from the cervical ganglia of the sympathetic trunk and the cardiac branches of the vagus and recurrent laryngeal nerves except those that supply the superficial cardiac plexus

# The Coronary Circulation

The coronary circulation refers to the vessels that supply and drain the heart

- The distribution of parasympathetic (vagal) nerve fibers to the ventricular coronary system is
- There is much more expensive sympathetic innervation of the coronary vessels
- Run in the respective atrioventricular groove
- Coronary arteries arise from the root of the aorta (aortic sinus)
- Coronary circulation fill during diastole it means that Blood flow to the heart occurs mainly during diastole.
- Blood supply of heart lies in subepicardial space
- Coronary blood flow is mainly determined by local oxygen demand.
- Coronary blood flow: the resting coronary blood flow is about 225ml/min which is about 0.7-0.8ml/gm of heart muscle, or 4-5% of cardiac output

# The Arterial Supply of the Heart

# 1) Right Coronary Artery (RCA): RMP

- RCA arises from the anterior aortic sinus
- It runs in AV groove and Anastomosis with LCA in posterior AV groove
- · If the right coronary artery is occluded distal to the origin of the right marginal artery, the blood supply to the AV node will be affected the most
- Large/Main branches:
  - ✓ Marginal artery
  - ✓ Posterior interventricular artery
- Typically The RCA supplies:
  - ✓ All conducting system except: Right Bundle Branch(RBB)
  - ✓ The Right atrium and most of the right ventricle
  - ✓ Inter-atrial septum
  - ✓ Post-inferior 1/3<sup>rd</sup> of the interventricular septum

# 2) Left Coronary Artery (LCA)

- It arises from the left posterior aortic sinus
- It is larger than RCA
- Left anterior descending artery—LAD, its blockage will cause infarction of apex of the heart
- The left coronary artery travels a short course between the left auricle and ventricle, and divided into two branches: anterior interventricular or left anterior descending artery and circumflex artery
- The anterior interventricular or LAD artery descends in the anterior interventricular sulcus and provides branches to anterior left ventricle wall, anterior two-thirds of the interventricular septum, bundle of His and apex of the heart
- Typical LCA supplies:
  - ✓ Anterior 2/3<sup>rd</sup> of the interventricular septum

  - ✓ The Left atrium and left ventricle.

# Posterior interventricular artery (PIVA):

- Most often called the posterior descending artery (PDA)
- It supplies the posterior third of the interventricular septum. The remaining anterior twothirds is supplied by the anterior interventricular artery which is a septal branch of the <u>left</u> anterior descending artery, which is a branch of the left coronary artery.
- In Right dominance, 90% PIVA is the branch of RCA

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Cardiovascular System

In Left dominance--- 10% PIVA is the branch LCA

- Artery of SA node:
  - √ 70% arise is from RCA
  - √ 30% arise from LCA
- 4) Important note on Aortic sinus:

An aortic sinus is one of the anatomic dilations of the ascending aorta, which occurs just above the aortic valve.

There are generally three aortic sinuses: (one anterior and 2 posterior sinuses):

- The left posterior aortic sinus gives rise to the left coronary artery.
- The anterior aortic sinus gives rise to the right coronary artery.
- Usually, no vessels arise from the right posterior aortic sinus, which is therefore known as the non-coronary sinus.

#### **Cardiac Veins**

# 1) Coronary sinus:

NAME AND POST OFFICE ADDRESS OF THE OWNER, WHEN PERSON NAMED IN COLUMN 2 IS NOT THE OWNER, THE OWNE

- . The coronary sinus drains into the right atrium, at the coronary sinus orifice, an opening between the inferior vena cava and the right atrioventricular orifice or tricuspid valve.
- The coronary sinus runs transversely in the left atrioventricular groove on the posterior side of the heart. It is the distal portion of the great cardiac vein feeding into the right atrium.
- The coronary sinus drain 2/3rd of the heart, predominantly drains the left ventricle and receives approximately 85% of coronary venous blood
- It is the continuation of the Great cardiac vein
- Guarded by the rudimentary nonfunctioning valve, The coronary sinus valve is also known as the Thebesian valve (also known as the valve of Vieussens)
- Sinus venosum develop into the coronary sinus
- Tributaries:
  - ✓ Great cardiac vein:
    - o The great cardiac vein begins at the apex of the heart
    - o It ascends in the Anterior interventricular groove
    - o Accompanied by LAD
    - o Clinically; the great vein reaches the ostium of the left ventricle at the level of the left fibrous trigone, thus the vein is prone to injury during mitral or aortic valve surgery.
  - Middle cardiac vein: PM
    - o It runs in Posterior interventricular groove
  - √ Small cardiac vein
    - Accompany marginal artery
  - ✓ Posterior cardiac vein:
    - o It either enters the coronary sinus directly or joins the great cardiac vein.
  - ✓ Oblique vein of the left atrium
- 2) Anterior cardiac vein

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- Drain directly into the right atrium
- Drain anterior surface of the right atrium and right ventricle
- 3) Venae cardis minimi: Small vein that lies in the muscle wall and can open directly into any chamber of the heart

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# Conduction and Conduction Pathway

#### Conduction velocity:

- Highest conduction (4m/sec)——Purkinje fiber—<u>Because of large diameter</u>
  - Lowest conduction(0.02-0.04m/sec)————AV node
- Conducting system of the heart lies in sub-Endocardium
- --intercalated disc Anatomic Conduction of heart-
- Energy for cardiac contraction:
  - ✓ Mainly from fatty acid
  - ✓ Partly from other nutrients e.g. lactate and glucose

# Conduction pathway:

- SA node (pacemaker——internodal fibers and atria——AV node (delay)——— --AV bundles (bundle of His)-----right and left branches------Purkinje fiber (from apex to base of ventricles)
- Bundle of His is the only pathway between atria and ventricle
- Structurally Purkinje fibers differ from the ordinary cardiac muscle fiber in the following respect:
  - Purkinje fibers have a large diameter
  - Usually have two centrally located nuclei
  - Contain relatively more Sarcoplasm rich in glycogen
  - Fewer myofibrils located in the periphery of fibers

# Atria, Ventricle and Purkinje System Action Potential

## Phase 0

- Rapid upstroke
- Na channel open

#### Phase 1

- The brief period of initial Repolarization
- K-Efflux

# Phase 2

- Plateau-Ca+ influx, K+ efflux
- During this phase outward and inward current is equal so membrane potential is stable

### Phase 3

- Rapid Repolarization
- Massive K<sup>†</sup> efflux

## Phase 4

- · Resting membrane potential
- The Period during which inward and outward current are equal and membrane potential approach the potassium equilibrium potential

# Absolute Refractory Period (ARP):

- During this period, the excitability of the cardiac muscle is completely lost
- No other stimulus, whether its strength can excite cardiac muscle
- Significance: due to long ARP, tetanus cannot be produced in cardiac muscle Tetanization of cardiac muscle is fatal because the heart as a pump must contract and

# Na' channels close Ca2+ channels close ABSOLUTE REPRACTORY Phase 4 PERIOD Resting potential a 2 m action potential cannot be initiated Leaky K\* channels Time (msec)

# Chapter 4

# Sinoatrial Node (SA Node)

- Located in the upper part of sulcus terminalis No wave for SA node on ECG, The SA node pacemaker activity is not observed on the ECG because the node is too small to generate electrical potential differences large enough to be
- Generate impulse at a faster rate

recorded from the body surface

- The pacemaker potential of SA node is due to slow Ca<sup>++</sup> channel
- SA node has the most prominent prepotential
- SA node activity decreased by the parasympathetic increase of potassium
- The sinoatrial (SA) node develops during week 5. It is part of the sinus venosus which becomes incorporated into the right atrium.
- The atrioventricular (AV) node also develops from the cells in the wall of the sinus venosus together with cells from the atrioventricular canal region.
- Normally, the rate of the heartbeat in human is determined by the SA node
- Rate of rhythmic discharge of excitatory and conducting system:
  - ✓ SA node-----70-80 times/min
  - AV node----- 40-60 times/min
  - ✓ Purkinje fiber-----15-20 times/min

# Action potential:

- ✓ Phase 0 = Upstroke---Opening of voltage-gated Ca<sup>++</sup> channel. These cells lack fast-voltage. gated Na+ channels. Result in a slow conduction velocity that utilized by the AV node to prolong transmission from the atria to the ventricle
- ✓ Phase 2: Plateau is absent
- ✓ Phase 4: Slow diastolic depolarization-----membrane potential spontaneously depolarize as Na<sup>+</sup> conductance increase. Accounts for the automaticity of SA and AV nodes. The slope of phase 4 determines the heart rate. Acetylcholine decrease and catecholamine increase the rate of diastolic depolarization, decreasing or increasing heart rate respectively

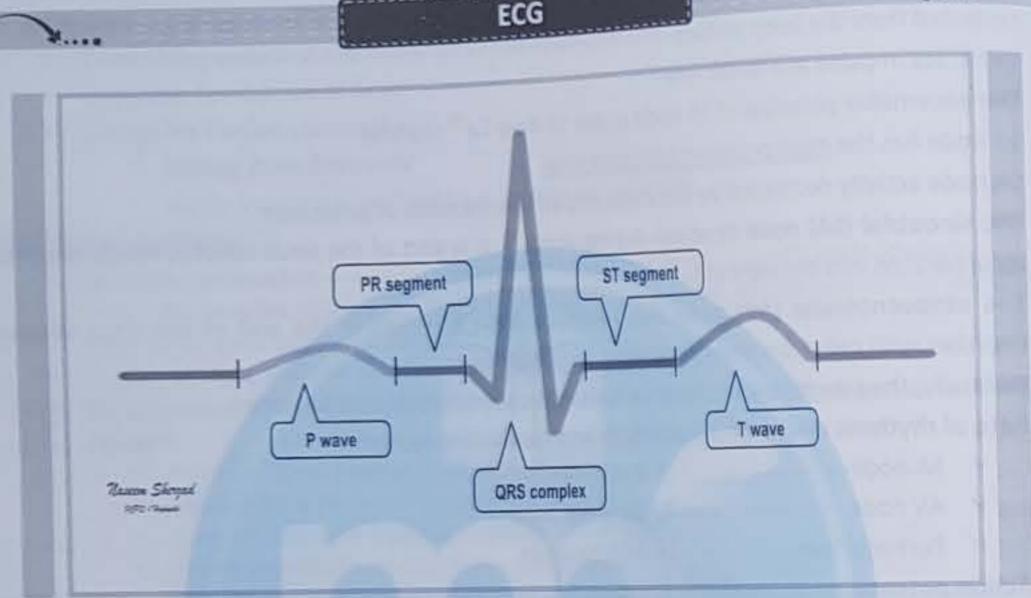
# Atrioventricular Node (AV Node)

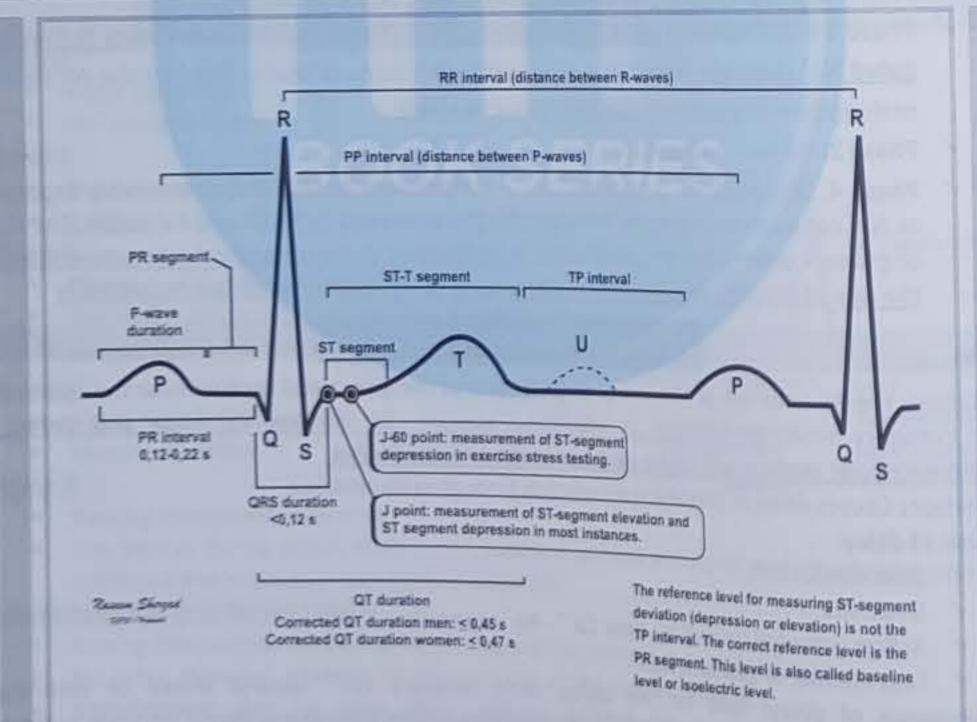


- Location: The AV node lies at the lower back section of the interatrial septum near the opening of the coronary sinus, perforation at interatrial septum can damage AV node and defect in interventricular septum will cause damage in the tricuspid valve.
- Function: Causes delay in impulse transmission from atria to ventricle
- Cause of delay:
  - ✓ Slow conduction
  - √ Small size
  - ✓ Action potential caused by slow Ca<sup>++</sup> Na<sup>+</sup> channels
  - ✓ Less number of gap junction
- Importance of delay: Due to this delay, atria contract 1/6th second ahead of ventricular contraction, which allows proper filling of ventricles before they pump blood into the aorta and pulmonary trunk.

TOLOGY

# PHYSIOLOGY





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# ...

- P-Wave:
   Indicate Atrial depolarization or atrial contraction
  - Tall in right atrial enlargement-----P-pulmonale
  - Bifid in left atrial enlargement-----P-mitral
  - Absent in AFib
  - In Junctional rhythm, P-wave is absent, inverted, buried or retrograde

# 2) PR-Interval: Normal: 180-220msec

- The PR-interval is from the start of the P-wave to the start of the Q-wave
- PR-interval show AV-nodal delay
- AFib occurs at the end of PR-interval or at the end of action potential
- Prolong PR-interval: Heart blocks, beta-blocker, calcium channel blocker
- Short PR-interval: WPW syndrome, tachycardia

## 3) PR-Segment:

- PR segment is, between the end of the P wave and ends at the start of the QRS complex.
- It corresponds to the <u>period between the end of atrial depolarization and the onset or</u>
   start of ventricular depolarization

# 4) QRS Complex:

- Depolarization of ventricle
- Time taken by nerve impulse to transmit Endocardium to Epicardium in ECG as QRS complex
- The QRS complex is prior to ventricular systole because the electrical activity is faster than mechanical effects that's why contractions occur after the wave
- The Low voltage QRS complex is seen in recurrent old MI

# 5) ST-Segment:

- The ST-segment is that portion of the ECG cycle from the end of the QRS complex (depolarization of ventricle) to the start of T-Wave (ventricular Repolarization)
- It represents the earliest phase of ventricular Repolarization
- ST-segment are usually Isoelectric and normal
- . It is due to the Influx of Calcium
- ST-segment elevation: in general, ST-segment elevation indicates infarction, which can be seen in pericarditis as well as Prinzmental angina. ST segment elevation in L4, artery which will be effected is LAD
- ST-segment depression: ischemia, hypokalemia/hypomagnesemia and digitalis effect

# 6) T-Wave:

- Represent the ventricular Repolarization

#### 7) QT Interval:

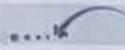
- Represent the entire period of ventricular depolarization and subsequent Repolarization, this duration reside between the beginning of QRS complex to the end of T-wave
- Anything which prolongs QT interval can pre-dispose to Torsades de pointes
- Prolong by: hypoglycemia, hypokalemia and hypomagnesaemia
- Shortened by: Hypercalcemia, digitalis
- Hypercalcemia cause------Cardiac arrest systole

# 8) U-Wave: (inconstant)

- Slow depolarization of papillary muscles
- More prominent in hypokalemia



# **Heart Sound**



Sounds heard via auscultation with a stethoscope of the closing of the atrioventricular valves ("lub") and semilunar valves ("dub")

### 1) First Heart Sound---S1

- Can be louder on decreasing PR interval
- Normal heart sound produced by closure of the mitral valves and tricuspid valves during isovolumetric contraction
- Short frequency, long duration (0.14 sec)
- Loud S1 causes: short PR interval, mitral stenosis, left atrial Myxoma
- Soft S1 causes: long PR interval, depress left ventricular function, left bundle branch block

## 2) Second Heart Sound-----S2

- High pitch, high-frequency sound & Short duration----- 0.11- 0.14 seconds
- Normal heart sound Produce by closure of the aortic and pulmonary valve
- S2 how splitting i.e. aortic valve close before pulmonic valve means delay closure of the pulmonary valve, under normal condition Inspiration Increase splitting and expiration minimize splitting
- · Wide splitting:
  - ✓ It is an exaggeration of normal splitting and seen in the condition that delays right ventricular emptying e.g. pulmonary stenosis and RBBB
- · Fixed splitting:
  - ✓ It means that in both inspiration and expiration aortic valve closes before pulmonary valves....seen in ASD

# 3) Third Heart Sound --- S3

- Produce during Rapid ventricle filling
- Due to loosening of Mitral Valve and Tricuspid Valve in heart failure
- It's normal in Pregnancy, children and young adolescent

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# Cardiovascular System

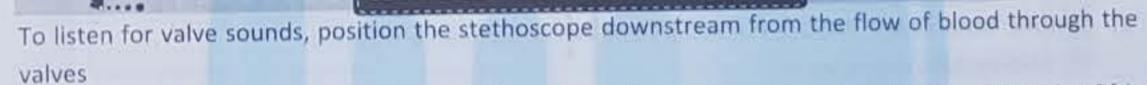
- In Adults, it's due to HF & DCM so pathological.
- Best heard at the apex (the apex of the heart is located in 5th ICS, 3.5 inches or 8-9 cm from midline)

## 4) Fourth Heart Sound----54

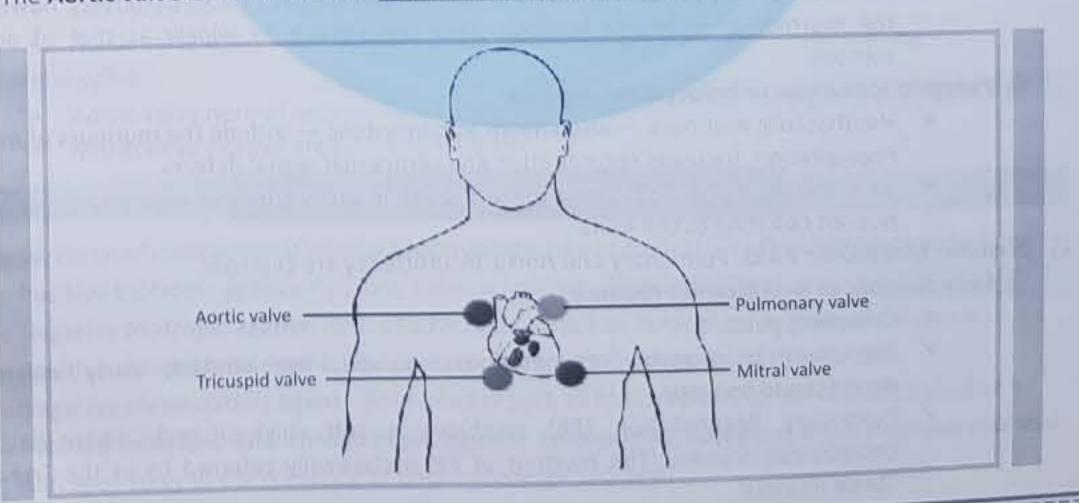
- Produced Due to atrial contraction/systole against a stiffed Ventricle like HCM and HOCM
- Best heard at left sternal border
- Always pathological sound
- Produced as a result of active ventricle filling against Pressure of HCM
- Absent in atrial fibrillation

Parameter	Inspiration	Expiration
Jugular venous pressure	Falls	Rises
Blood pressure	Falls (Up to 10 mmHg)	Rises
Heart rate	Accelerates	Slows
Second heart sound	Splits	Fuses

# Where to listen for heart sounds



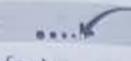
- The Tricuspid valve is heard just to the left of the lower part of the sternum near the fifth intercostal space.
- 2) The Mitral valve is heard over the apex of the heart in the left fifth intercostal space at the midclavicular line.
- The Pulmonary valve is heard over the medial end of the left second intercostal space.
- The Aortic valve is heard over the medial end of the right second intercostal space.



# Cardiovascular System

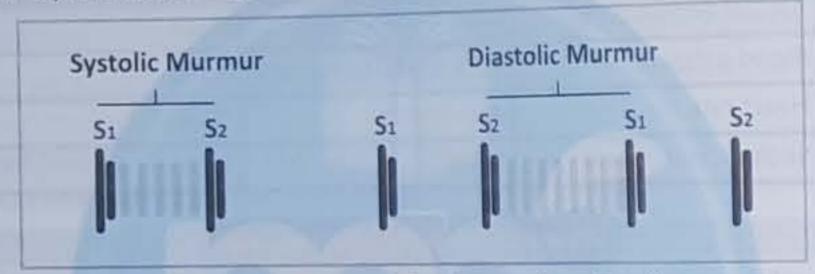
# Chapter 4

# Murmurs



Unusual heart sound detected by auscultation; typically related to septal or valve defects

- A murmur is either systolic, diastolic or continuous throughout systole and diastole. Remember that systole occurs between the S1 and S2 heart sounds, whereas diastole occurs between S2 and
- \* Stenosis of the aortic or pulmonic valves will result in a systolic murmur as blood is ejected through the narrowed orifice. Conversely, regurgitation of the same valves will result in a diastolic murmur as blood flows backward through the diseased valve when ventricular pressures drop during relaxation. Regarding the mitral and tricuspid valves, stenosis would result in a diastolic murmur and regurgitation a systolic murmur.
- A pictorial representation of systolic and diastolic murmurs is below.



1) Systolic: Mnemonic: PASS---Pulmonary and Aortic Stenosis are Systolic

# Mid-systolic murmur:

- ✓ Midsystolic murmurs also known as systolic ejection murmurs, or SEM include the murmurs of aortic stenosis, pulmonic stenosis, hypertrophic obstructive cardiomyopathy and atrial septal defects.
- Crescendo—decrescendo murmurs (diamond or kite-shaped murmurs), progressive increase in intensity is followed by a progressive decrease in intensity, occur in aortic stenosis and Radiating to the neck and back
- The murmur of pulmonic stenosis is very similar to that of aortic stenosis; however, the murmur of pulmonic stenosis does not radiate as widely as that of aortic stenosis.

# Pansystolic murmur or holosystolic murmur:

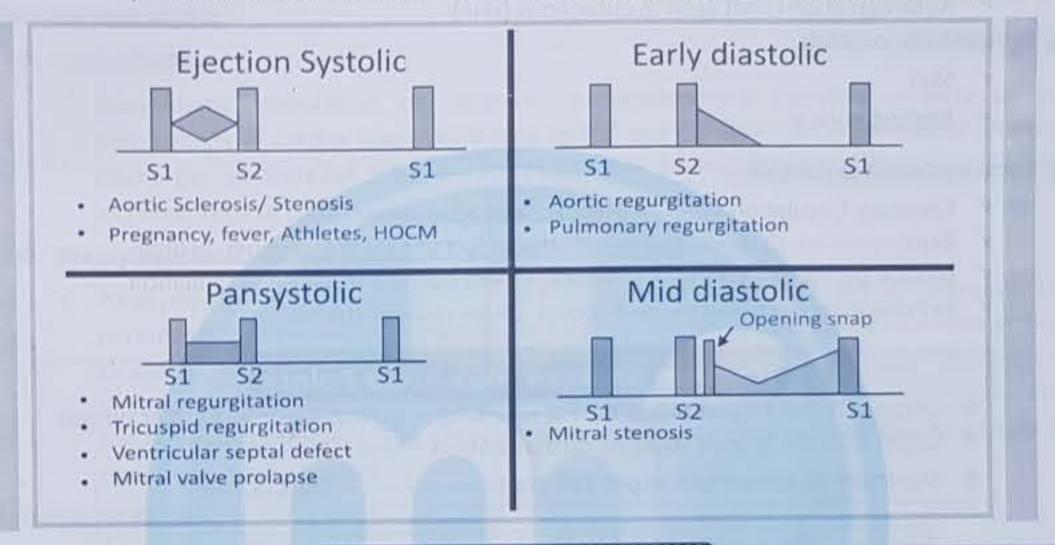
- ✓ Holotsystolic murmurs also known as pansystolic include the murmurs of mitral regurgitation, tricuspid regurgitation and ventricular septal defects.
- in mitral regurgitation murmur Radiating to the axilla, tricuspid regurgitation is same but not radiating to the axilla
- Diastolic: Mnemonic: PAID: Pulmonary and Aortic Insufficiency are Diastolic Early diastolic or decrescendo murmur:
  - Collapsing pulse
  - The murmur of aortic regurgitation is a soft, high-pitched, early diastolic,
  - Pulmonary Regurgitation (PR) produces a soft, high-pitched, early diastolic decrescendo murmur. The murmur of PR is classically referred to as the Graham-

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# Cardiovascular System

# Mid diastolic murmur

- ✓ Occur in mitral stenosis, the severity of mitral stenosis clinically detected by the length of diastolic murmur
- The opening of the mitral valve produces an "opening snap" or Rumbling sound
- The ECG finding in mitral stenosis is often normal early in the disease. The most common finding is left atrial enlargement (p-mitral), however this finding disappear if patient enter atrial fibrillation (no P-wave, rhythm is irregularly irregular---irregular RR)



# Values and Facts

# 1) Pressure in the various chamber of heart:

- Right atrium-----0-4 mmHg
- Left atrium----8-10 mmHg
- Right ventricle----- 8/4 -----Pulmonary artery----25/10
- Left ventricle-----120/10---Aorta-----120/80
- Aortic valve open when it exceeds the ventricular pressure of------80 mm Hg

# 2) Normal valve

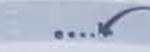
- Aortic valve normal area-----2.5-4.5 cm<sup>2</sup>
- Mitral valve normal area-----4-6 cm

# Inotropic and Chronotropic Effects And Agents

Inotropy: Force of contraction (Systolic), Chronotropy: rate of contraction, Dromotropy: conduction

- Positive Inotropic agents: Calcium, Catecholamines, Digoxin, caffeine
- Negative Inotropic agents: Beta-blocker, acetylcholine, Potassium, acidosis and hypoxia
- Positive chronotropic agent: Atropine, dopamine, Dobutamine And epinephrine
- Negative chronotropic agent: Beta-blocker such as Metoprolol, Digoxin and acetylcholine
- Positive Inotropic and chronotropic agents: Epinephrine, Norepinephrine, Isoproterenol and Glucagon (only in the presence of beta-adrenergic blocked)

# Control Of Special Circulation Of Blood



# Autoregulation:

- ✓ The capacity of the tissue to regulate/maintain their own blood supply is known as
- Autoregulation is well developed in the kidney, but It has also been observed in the mesentery, skeletal muscle, Brain, Liver and heart, except skin
- ✓ Autoregulation is not seen in cutaneous (skin)
- Sympathetic control:
  - √ Skin
  - Resting muscle
- Local metabolites control:
  - ✓ Coronary Circulation——Hypoxia and adenosine
  - ✓ Brain—————CO2, H+, the vasodilator effect of CO2 is maximum in brain
  - ✓ Muscle during <u>exercise</u>—Lactate, K and adenosine, cause vasodilation
  - ✓ In Pulmonary circulation——hypoxia cause vasoconstriction

# Naseem Sherzad High-Yield Points

- Organ with the largest blood flow——lung——5L/min, same as Cardiac output
- Organ with the largest share of cardiac output ——Liver
- ❖ Maximum O₂ consumption per 100 gram— --- Heart (9.7ml)

# The organ which has maximum oxygen consumption

- ---250ml/min Whole body-----
- ---51ml/min
- ❖ Skeletal muscle———50ml/min
- -49ml/min or 20% of total body oxygen \* Brain -

## Organ with highest flow per gram

- Carotid body: ——2L or 2000ml /min/100gm tissue
- ---360ml/min/100gm tissue kidney:----
- -300ml/min/100gm tissue Adrenal gland-
- -95ml/min/100gm tissue Liver----
- --50ml/100mg, · Brain:--
- ❖ Brain auto regulatory pressure—50-150mm Hg, in an adult, cerebral blood flow (CBF) is typically 750 millilitres per minute or 15% of the cardiac output.
- Organ with largest AV O2 difference is-----

-Kidney

- Organ with minimum AV O2 difference is-
  - **During Exercise**
- ◆ Decrease 0₂ flow to----Muscle
- Decrease blood flow to-
- No effect on --Brain

Chapter 4

Cardiovascular System

# Regulation of Heart Rate



# Local mechanism:

It includes SA nodes that generate and transmit rhythmic self-excitatory cardiac impulses to cause heart rate 72 times per min, in adult males. so, any factor that locally acts on SA node to change its rhythmicity can also change heart rate

# Nervous mechanism

## Sympathetic:

✓ Sympathetic stimulation of heart-----nor-epinephrine secreted-----increase the permeability of cardiac fiber membrane to Na<sup>+</sup> and Ca<sup>+</sup>-----increase rate of SA nodal discharger so increase HR-----increase rate of impulse transmission ----increase force of contraction

## · Parasympathetic

✓ Parasympathetic stimulation of heart-----acetylcholine released-----increase the permeability of cardiac fiber membrane to K\*-------Hyperpolarization------longer time to reach the threshold by Na+ leakage-----decrease rate of SA nodal discharge so decreases Heart Rate------decrease rate of impulse transmission------decrease the force of contraction. The parasympathetic nervous system decreases heart rate by opening potassium gates

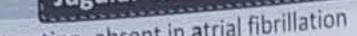
# a Intrinsic heart rate:

- . Intrinsic heart rate is defined as the rate at which the heart beats when all cardiac neural and hormonal inputs are removed
- Intrinsic heart rate is determined by IV administration of atropine and Atenolol

# Pulse Pressure

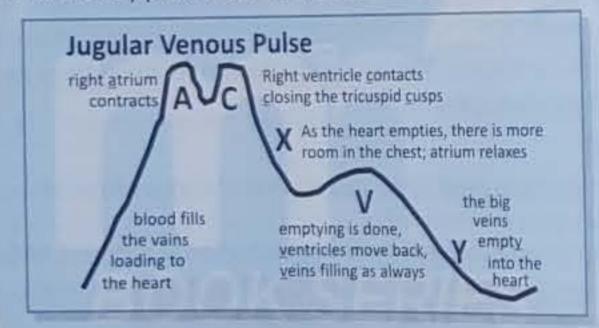
- It is the difference between systolic and diastolic pressure (120-80= 40 mm Hg)
- The most important determinant of pulse pressure is Stroke Volume
- In the patent of ductus arteriosus, the pulse pressure is increasing due to an increase in systolic pressure and a decrease in diastolic pressure
- Dicrotic notch or incisura: A notch in the recording of pressure pulse curve is called Dicrotic notch which is caused by the closure of the aortic valve
- Extra-systolic beat: on the extrasystolic beat, a pulse pressure decrease because there is inadequate ventricular filling time means the ventricle beats "Too Soon", as a result, stroke volume also decrease. The next "normal" ventricular contraction that occurs after extra-systole would produce increased pulse pressure because the contractility of the ventricle is increased
- The Pulse pressure increase in:
  - √ Thyrotoxicosis
  - ✓ Pulse pressure increase when the capacitance of the arteries decreases such as with aging caused by arteriolosclerosis
  - ✓ In aortic regurgitation, the pulse pressure is increasing due to decrease diastolic pressure and increase systolic pressure

# Jugular Venous Pulses (JVP)





- x descent: atrial Relaxation
- y decent: Blood flow from RA to RV ----- EmptYing of RA
- v wave: the increase in the right atrial pressure due to filling against closed tricuspid valve ---Filling (Villing) of the right atrium
- c wave: Right ventricle contraction
- Difference between the Jugular vein and carotid artery pulsation
  - Carotid is one pulsation per heart beat and jugular is two pulsations per heart beat (biphasic waveform, a + v wave)
  - Carotid is palpable while jugular is impalpable
  - Carotid is independent of respiration while in healthy heart JVP decrease on inspiration and in unhealthy (pericarditis) JVP increase on inspiration
  - The Carotid pulse is independent of respiration, position and abdominal pressure while in the jugular height of pulsation varies with respiration, varies with the position of the patient and rise with abdominal pressure
  - ✓ In carotid, pulsation is unaffected by pressure at the root of the neck while in the jugular, pulsation diminished by pressure at the root of the neck



# **Ventricular Filling**

# 1) Rapid filling phase:

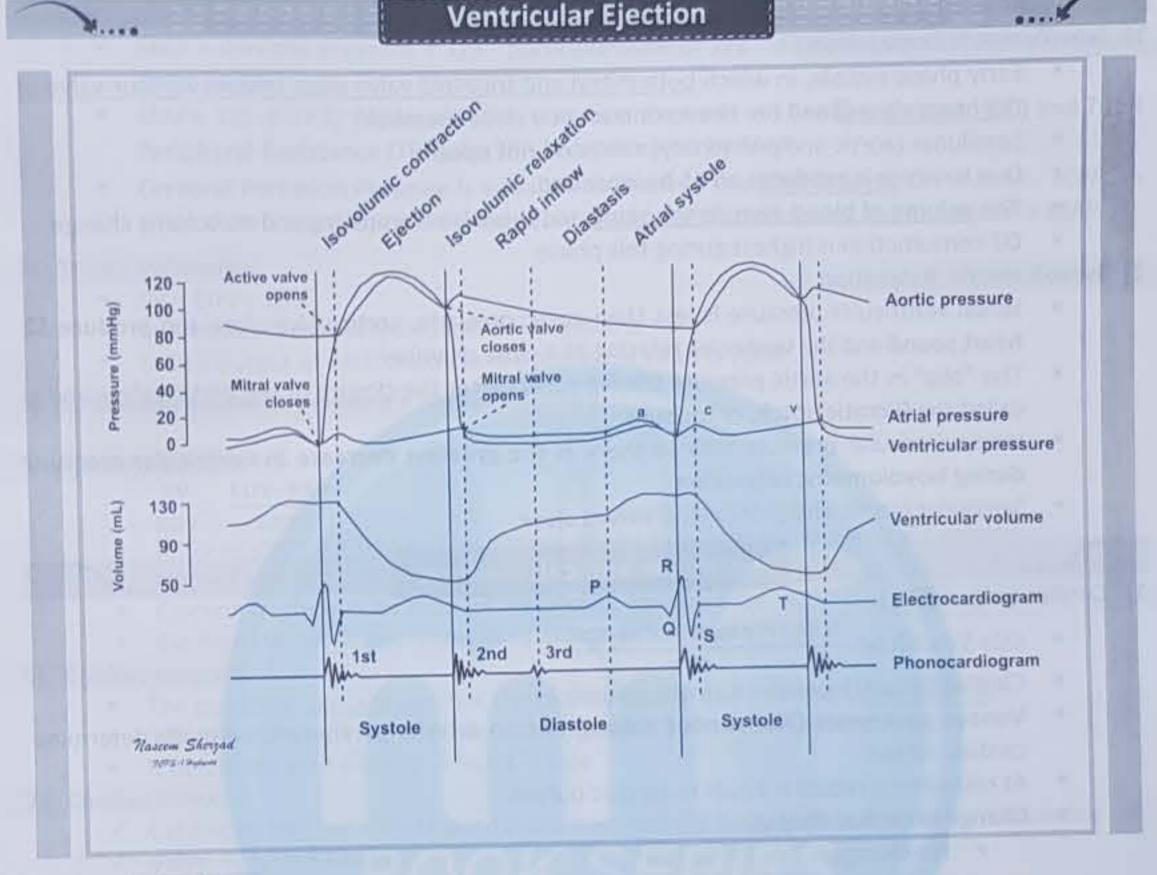
- It is Initial phase, Passive filling of the ventricle occurs
- During this phase, atrial pressure becomes greater than intra-ventricular pressure
- AV valves (tricuspid and mitral) open, and blood flow rapidly into the respective ventricle.
- 80% filling of ventricle occurs in this stage
- 3<sup>rd</sup> heart sound produced
- During the rapid filling phase, there is the lowest aortic pressure.
- During mid diastole of the cardiac cycle, the pressure in the ventricle is lowest

# 2) Slow filling phase:

- Atrial contraction/atrial systole/active phase. The Longest phase of the cardiac cycle
- 20% filling, contribute to but not essential for, ventricular filling
- In ventricular hypertrophy, filling of the ventricle by atrial systole causes the 4<sup>th</sup> heart
- P-wave on ECG and "a" wave on the venous pulse curve
- Maximum blood present in ventricle during this stage
- Pressure and volume transfer to ventricles

Chapter 4

Cardiovascular System

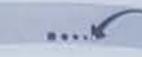


# 1) Rapid ejection:

- Ventricular pressure reaches its maximum value during this phase.
- 70% emptying occur in rapid ejection
- C wave on venous pulse occurs
- When Ventricular pressure is greater than aortic pressure the aortic valve open--ventricular pressure greater than 80 mm Hg causing the opening of the aorta
- Most of the stroke volume ejected during this phase
- Increase PR-interval decrease rapid ejection

# 2) Slow ejection:

- 30% emptying occurs in slow ejection
- Ventricular pressure begins to decrease, aortic pressure also decrease
- Maximum aortic pressure in this stage
- Represent T-wave on ECG
- Least amount of blood present in ventricle
- It is important to note that Blood flow during ventricular filling is mostly depend upon pressures changes



# Isovolumetric Contraction

- Early phase systole, in which both mitral and tricuspid valve close (means All four-valve of the heart closed) and the heart contract as a close chamber
- Semilunar (aortic and pulmonary) valves do not open
- Due to which it produces an S1 heart sound
- The volume of blood remain the same and there is no emptying and no volume change
- O2 consumption is highest during this phase

# 2) Isovolumetric Relaxation

- When ventricular pressure is less than aortic pressure, aortic valve close and produce S2 heart sound and the ventricles relaxing as a close chamber
- The "blip" in the aortic pressure tracing occurs after the closure of the aortic valves and is called the Dicrotic notch, or incisura.
- Intra-ventricular pressure falls so there is the greatest decrease in ventricular pressure during isovolumetric relaxation
- Semilunar (aortic and pulmonary) valves close

# Formulas and calculations

### Cardiac output (CO):

. CO=SV x HR or

MAP-right atrial pressure

- Cardiac output depends on stroke volume
- Venous parameter (like venous return) not an arterial parameter, normally determine cardiac output
- At rest venous return is equal to cardiac output
- Change in cardiac output:

# ✓ No-change:

- o Sleep
- o A moderate change in environmental temperature

#### Increase:

- Anxiety and excitement -----50-100%
- o Eating------30%
- o Exercise-----up to 700%
- o High environmental temperature
- o Pregnancy
- o Epinephrine

#### Decrease

- Sitting or standing from lying position ----- 20-30%
- Rapid arrhythmia
- Heart disease
- o HTN: Hypertension decrease cardiac output by directly causing an increase in
- Measurement of cardiac output:
  - ✓ Oxygen Fick method
  - ✓ Indicator dilution method: Dye used in indicator dilution method is cardio-green

# Chapter 4

Cardiovascular System

# 2) Mean arterial pressure (MAP):

- MAP = diastolic pressure + 1/3<sup>rd</sup> pulse pressure or 2/3<sup>rd</sup> diastolic pressure + 1/3<sup>rd</sup> systolic pressure OR
- MAP= CO X TPR, Mean arterial pressure depends on Cardiac Output (CO) and Total Peripheral Resistance (TPR), So TPR is determined by MAP
- Cerebral Perfusion Pressure is equal to MAP when the dura is open. CPP = MAP ICPP, so when dura is open, the ICP will be equal to atmospheric pressure and hence CPP = MAP

## 3) Stroke Volume=

- SV = EDV ESV
- In athlete at rest has increased stroke volume
- Stroke output of each ventricle in the normal adult is 70ml
- 4) Stroke work= Aortic pressure x Stroke volume

### 5) Ejection fraction=

- SV EDV-ESV EDV
- If the ejection fraction increase there will be a decrease in end-systolic volume
- Normal ejection fraction is 50-75%
- Ejection fraction is an index of ventricular contractility
- Ejection fraction is decreases in systolic heart failure

## 6) Cardiac reserve:

- The maximum percentage that the cardiac output can increase above normal
- 300-400 percent, in athletically trained person 500 to 600 percent or more
- It decreases with all type of heart failure

# 7) Cardiac index:

- ✓ Cardiac output per minute per square meter of the body surface is called cardiac index
- √ Valve: 5/1.7 = 3 Liter/m²

# 8) Reynolds's number:

- Predicates whether blood flow will be laminar or turbulent
- When Reynolds's number is increased, there is a greater tendency for turbulence

# $Re = vd\rho/\eta$

- √ V----is the velocity of the fluid,
- ✓ P----is the density of the fluid,
- ✓ η----is the viscosity of fluid,
- √ d----is the length or diameter of the fluid.

# 9) Resistance, pressure and flow:

# 8η (viscosity) Legnth

- Resistance is directly proportional to viscosity and vessels length and inversely proportional to the radius to the 4th power
- Example: A 53 years old woman is found, by arteriography, to have 50% narrowing of her left renal artery. What is the expected change in blood flow through the stenotic artery? Answer: if the radius of the artery is decreased by 50% (1/2), then resistance would increase by 24 or 16. Because blood flow is inversely proportional to resistance (Q= P/R). the flow will decrease to 1/16 of the original value
- Viscosity:

# Cardiovascular System

# Chapter 4

- ✓ It is the resistance offered by blood to its own flow
- ✓ Viscosity increase in Polycythemia, hereditary spherocytosis, DM, acidosis, hyperglycemia) and decrease in anemia, malaria, exercise and edema

# 10) Cardiac Cycle:

- Heart rate = 75/min
- Hence Duration for one cycle is= 60/75 = 0.8 sec (cardiac cycle duration in man)
- If heart rate double than cardiac cycle duration will be = 60/150 = 0.4 sec
- Absolute period when the whole heart is in diastole is 0.4 sec
- Atrial cycle:
  - -0.1 sec ✓ Atrial systole -
  - \_\_\_\_0.7 sec √ Atrial diastole—
- Ventricular cycle:
  - √ Ventricular systole ----- 0.3 sec
  - √ Ventricular diastole——0.5 sec

# Preload, Afterload, End-Diastolic Volume (EDV) and Venous Return

# Preload: Same as end-diastolic volume

- ✓ Ventricular preload is measured by EDV means ventricular EDV is the best indicator of preload
- ✓ VEnodilators e.g. nitroglycerine—decrease prEload

## Afterload:

- ✓ Mean arterial pressure (proportional to peripheral resistance)
- ✓ VAsodilator (e.g. hydrAlazine)—decrease After load –Arterial

# End-diastolic volume:

- ✓ It is the volume of blood in the right and/or left ventricle at end load or filling in (diastole) or the amount of blood in the ventricles just before systole.
- ✓ Depend on venous return (increase by contraction of calf muscle of leg and decrease by calf muscle paralysis)
- ✓ The most important factor for stretching of cardiac muscle is end-diastolic volume.
- ✓ End-diastolic volume------110-120ml

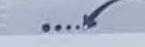
# Venous return:

- . It is the volume of blood flowing from veins into right atrium each min
- Formula: MSFP-RAP/RVR
- Value: VR=CR
- Different factors that regulate venous return are:
  - ✓ Mean systemic filling pressure (MSFP)——(directly proportional)
  - ✓ Right atrial pressure (RAP)—— (directly proportional)
  - ✓ Pressure gradient i.e. difference between mean systemic filling pressure and right atrial pressure (directly)
  - ✓ Resistance to venous return (RVR)--- (inversely)
  - ✓ Sucking effect of negative intra-thoracic pressure during inspiration

## Chapter 4

Cardiovascular System

**Effects of Ions and Temperature on Heart** 



# K tions:

When potassium ion conc. In ECF increase

- ✓ Heart becomes dilated, Heart rate decrease
- Impulse transmission through AV bundles blocks
- Heart becomes weak
- Heart rhythm becomes abnormal
- All these events lead to death

# Cattion:

- ✓ Increase Ca<sup>++</sup>: Causes spastic contraction of heart
- Decrease Ca++: Causes cardiac flaccidity

# A Nation:

✓ Increase Na<sup>+</sup> depress cardiac contraction of heart because Na<sup>+</sup> compete Ca<sup>+</sup> in contractile process

## Temperature:

- ✓ A moderate increase in temperature increase contractile strength of heart
- ✓ Prolong increase in temperature exhausts metabolic system of the heart and cause cardiac weakness

# General Structure of Blood Vessel

- √ It is Innermost layer
- ✓ Consist of endothelium and a thin layer of loose connective tissue called subendothelial layer
- ✓ Internal elastic lamina separating intima from media. It is a layer of elastic fiber

# Tunica Media:

Marica Intima

- ✓ It is the Middle layer
- ✓ The external elastic lamina may be present at the junction of media and adventitia
- ✓ External elastic lamina is <u>absent in large arteries like aorta</u>
- ✓ Tunica media is absent in berry aneurysm

# Tunica adventitia:

- ✓ Outer layer
- ✓ Baroreceptors are located in tunica adventitia
- Small blood vessels in the wall of blood vessels is known as vasa vasorum.
- Pericytes are mural cells surrounding blood vessels, adjacent to endothelial cells
- Capillaries have normally associated perivascular contractile cell called----pericytes

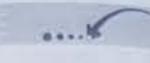
# Age-associated CVS changes:----Geriatric----old people

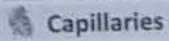
- ✓ Arterial wall thickening and stiffening, decrease venous compliance
- ✓ Systolic hypertension

# Weins without valve: IPSS

- -----Internal jugular vein
- -Pulmonary vein
- -----Superior vena cava -----Sinuses of brain
- Arteries don't have valves

# Facts about Vascular System (Histology)

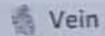




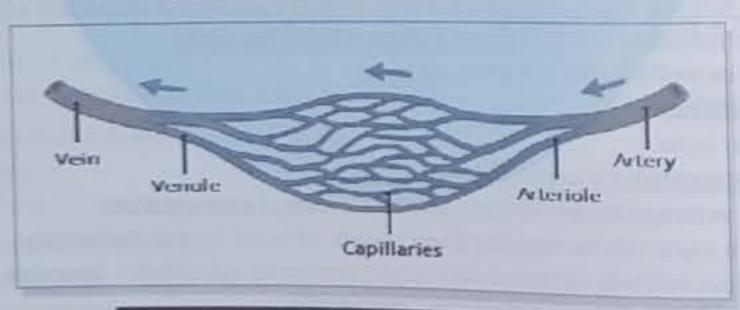
- The Maximum total cross-sectional area
- Site of gas exchange
- Minimum blood flow velocity
- Site of Second maximum vascular resistance (after arterioles)

# Arteriole:

- Minimum blood volume Is contained by arterioles
- Maximum vascular resistance occurs in Arterioles
- Arterioles receive autonomic nervous system innervation and respond to various circulating hormones in order to regulate their diameter
- The smallest vessels which may be just visible to the naked eye is arteriole (about 0.3mm) diameter)



- Larger and more complaint (stretchable) than arteries
- The Function of veins:
  - ✓ Can dilate to store blood, That's why Maximum blood volume Is contained by Veins
  - Can constrict to make stored blood available when it needs by the other part of the circulation
  - ✓ Regulate cardiac output
  - ✓ Transport blood from peripheral tissue back to the heart
  - √ 60% of blood volume at rest is in systemic veins and venules and function as blood a reservoir, that's why vein and venules are the biggest reservoirs of the blood
- · Venules are capillaries, which lack smooth muscle, are not directly innervated by sympathetic nerves
- . The moderator band (also known as septomarginal trabecula) is a muscular band of heart tissue found in the right ventricle of the heart.



	Naseem Sherzad High-Yield	Points
٠	Minimum total cross-sectional area	Acuto
2	Maximum blood pressure	
-	Minimum blood pressure	11.00
9	There is no arteriovenous anastomoses in-	Brain
10.0	Maximum pressure dissination	
*	Fluid which has 0.5g/dl protein-	Lymph

Chapter 4

Cardiovascular System

Gravity, Exercise, and Hemorrhage

# **Summary Of Responses To Standing**

Parameter	Initial response to standing	Compensatory response
Arterial blood pressure	Decrease	Increase (toward normal)
Heart rate		Increase
Cardiac output	Decrease	Increase (toward normal)
Stroke volume	Decrease	Increase (toward normal)
TPR		Increase (due to alpha-1 receptor activation, cause vasoconstriction)
Central venous pressure	Decrease	Increase (toward normal)

Compensatory mechanism: Compensatory mechanism will attempt to increase blood pressure toward normal. The carotid sinus Baroreceptors respond to the decrease in arterial pressure by decreasing the firing rate of the carotid sinus nerve. A coordinated response from the vasomotor center then increase sympathetic outflow to the heart and blood vessels and decrease parasympathetic outflow to the heart. As a result, heart rate, contractility, TPR, and venous return increase and blood pressure increase toward normal.

# Summary Of Effect Of Exercise

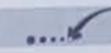
Parameter	Effect	
Heart rate	个个	
Stroke volume	<u>↑</u>	
Cardiac output	<b>个</b> 个	
Arterial pressure	个(slight)	
Pulse pressure	个(due to increased stroke volume)	
TPR	↓↓ (due to vasodilation of skeletal muscle beds)	
AV 02 difference	↑↑(due to increased O2 consumption)	

# Summary of a compensatory response to hemorrhage

Summary of a compens	Compensatory response
Parameter	1
Heart rate	1
Contractility	1
TPR	<b>*</b>
Vasoconstriction	<b>*</b>
Renin	
Angiotensin II	1
Aldosterone	*
ADH	*

- When BP becomes above normal:
  - Increase carotid sinus and aortic arch receptors potential
  - Increase the rate of firing in afferent nerves
  - Effect on the cardiovascular system:
    - ✓ Decrease sympathetic cardiac nerve activity
    - ✓ Decrease sympathetic vasoconstriction nerve activity
    - ✓ Increase parasympathetic nerve activity
  - Result in:
    - Decrease SV, HR, CO, TPR
    - ✓ Blood pressure decreased toward normal
  - When BP becomes below normal
    - Decrease carotid sinus and aortic arch receptors potential
    - Decrease rate of firing in afferent nerves
    - Effect on the cardiovascular system:
      - ✓ Increase sympathetic cardiac nerve activity
      - ✓ Increase sympathetic vasoconstriction nerve activity
      - ✓ decrease parasympathetic nerve activity
    - · Result in:
      - ✓ Increase SV, HR, CO, TPR
      - ✓ Blood pressure increased toward normal.

# Central Venous Pressure (CVP)



Cardiovascular System

- Considered a direct measurement of the blood pressure in the right atrium and vena cava
- Normal CVP is 2-6 mm Hg
- CVP elevated by: A decrease in cardiac output either due to decreased heart rate or stroke volume e.g. in ventricular failure
- CVP decreased by: Hypovolemic shock from hemorrhage, fluid shift, dehydration
- Indication:

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- √ Volume resuscitation
- ✓ Emergency venous access
- ✓ Nutritional support
- ✓ Administrating Hyperalimentation, caustic agent, or other concentrated fluid
- ✓ Central venous pressure monitoring
- Complication:
  - ✓ Pneumothorax: The incidence is thought to be higher with subclavian vein catheterization. In the case of catheterization of the internal jugular vein, the risk of Pneumothorax is minimized by the use of ultrasound guidance.
  - Bloodstream infection: All catheters can introduce bacteria into the bloodstream, but CVCs are known for occasionally causing Staphylococcus aureus and Staphylococcus epidermidis sepsis.

# Pulmonary Capillary Wedge Pressure (PCWP)



- It provides an indirect estimate of left atrial pressure (LAP)
- Although left ventricular pressure can be directly measured by placing a catheter within the left ventricle, it is not feasible to advance this catheter back into the left atrium.
- LAP can be measured by placing a special catheter into the right atrium then punching through the interatrial septum; however, for obvious reasons, this is not usually performed because of damage to the septum and potential harm to the patient
- PCWP is measured by inserting balloon-tipped, multi-lumen catheter (Swan-Ganz catheter) into a peripheral vein (e.g., jugular or femoral vein), then advancing the catheter into the right atrium, right ventricle, pulmonary artery, and then into a branch of the pulmonary artery.
- It is helpful to measure PCWP to diagnose the severity of left ventricular failure and to quantify the degree of mitral valve stenosis.
- PCWP is also important to measure when evaluating pulmonary hypertension.
- PCWP is also useful in evaluating blood volume status when fluids are administered during hypotensive shock. One practice is to administer fluids at a rate that maintains PCWP between 12-14 mmHg.
- it is considered the gold standard for determining the cause of acute pulmonary edema
- Elevated pulmonary capillary wedge pressure strongly suggests failure of left ventricular output
- Normal capillary wedge pressure-----4-12 mm Hg
- Swan-Ganz catheterization is the passing of a thin tube into the right side of the heart and the arteries leading to the lung. It is done to monitor the heart function and blood and pressure in and around the heart

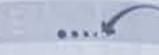
# Chapter 4

# Cardiovascular System

NASEEM SHERZAD FCPS -1 HIGH-YIELD

# PATHOLOGY

# Rheumatic Heart Disease (RHD)



# Aschoff bodies: Aschoff bodies are Pathognomonic and occur only in the heart of individuals with rheumatic fever. They result from inflammation in the heart muscle and are characteristic of rheumatic heart disease. Fully developed Aschoff bodies are granulomatous structures consisting

of <u>fibrinoid necrosis</u>, lymphocytic infiltration, occasional plasma cell and characteristically abnormal macrophage surrounding necrotic centers. Some of these macrophages fuse to form

Anitschow cell: These are enlarged macrophages also called caterpillar cells so named because of the appearance of their chromatin. Anitschow cell are activated histocyte

Fish mouth or button-hole stenosis (Stenosis of the mitral valve).

McCollum plaques present in rheumatic Endocarditis

Heart valve most common involved:

THE RESIDENCE OF SHARP SHAPE OF SHAPE O

----75-80% (Cause Mitral regurgitation in the acute case and ✓ Mitral valve mitral stenosis in chronic case)

✓ The Aortic valve is------30%

✓ Tricuspid and pulmonary -----5%

The Diagnostic test is blood culture and the initial best test is ASO titer

The most common cause of early death in the patient with acute rheumatic fever is Myocarditis and the most common initial presentation of acute rheumatic fever is migratory Polyarthritis. ----

# Jones criteria for Rheumatic fever

Major Criteria	Minor Criteria
Migratory Polyarthritis	Fever
Carditis	Arthralgias
Subcutaneous nodules	Elevated ESR and CRP
Erythema marginatum –skin rash	First degree AV block
Sydenham chorea	Leukocytosis

# Infective Endocarditis

- Splinter hemorrhage under fingernails
- Osler's nodes----painful micro lesion on fingers or toe pads
- Janeway lesion---- (they are small, flat, erythematous non-tender maculae on thenar and hypothenar eminence), painless microemboli in palms and soles
- Splenomegaly, fever, petechiae,
- Roth's spots----(Retinal hemorrhage with the white or pale center) and Haematuria
- Vegetations:
  - ✓ The endothelial damage by infection leads to the deposition of platelets and fibrin.
  - ✓ This mass that composed of fibrin, platelets and infecting organism is called vegetation.

# Eisenmenger' Syndrome



The process in which prolonged left to right shunt cause increased flow through pulmonary vasculature causing pulmonary hypertension. This in turn causes increased pressure in the right side of the heart and causes the reversal of the shunt into a right to left shunt.

- This reversal of left to right shunt into right to left shunt is called Eisenmenger' syndrome
- Mostly caused by ASD, VSD or less commonly by PDA

# Kawasaki Disease (Mnemonic CRASH)



Just imagines that less than four-year-old child is driving a motor cycle in cold weather. This will cause the following changes.

- Conjunctivitis (bilateral) also C means affecting Coronary vessels
- Rash (primarily on the trunk)
- Asymmetrical cervical lymphadenitis
- Strawberry tongue
- Hand and foot, show edema.

# Congenital Heart Disease: Cyanotic heart disease

- Early Cyanosis Blue Baby With 5T's ------Right to left shunt---5T's
- ✓ T-----Tetralogy of fallot (most common cause of early cyanosis)
- ✓ T-----Transposition of great vessels (Associated with maternal DM)
- ✓ T-----Truncus arteriosus (Pulmonary trunk fail to divide)
- ✓ T-----Tricuspid Artesia
- ✓ T-----Total anomalous pulmonary venous return
- Late Or Delay Cyanosis Blue Kids -----Left to right shunt--3D's (D also means delay)
  - ✓ D------VSD-----(Pansystolic murmur or Holosytolic murmur)
  - ✓ D-----(S2 sound shows fixed splitting)
  - ✓ D-----PDA-----(Close with indomethacin, peripheral cyanosis)

# Tetralogy of Fallot (TOF)

# Mnemonic: PROved=e=s = PRO-vsd

- P------Pulmonary stenosis (most important determinant for prognosis)
- R------Right ventricular hypertrophy
- O-----Overriding of the aorta
- VSD-----VSD
- Important to note:
  - ✓ Boot-shaped heart: X-ray show large right ventricle and small pulmonary artery which described as "boot-shaped" heart
  - ✓ Older patients historically learned to squat to relieve cyanotic symptoms in TOF.
  - ✓ Tetralogy plus ASD is called Pentalogy of fallot
  - ✓ TOF is the most common cyanotic congenital heart disease which is compatible with life
  - ✓ TOF is the most common cyanotic congenital anomaly observed in the adult.

# Chapter 4

- Coarctation of the aorta is associated with bicuspid aortic valve and turner syndrome.
- Infantile type or Preductal:

  - ✓ Aortic stenosis is proximal to the insertion of ductus arteriosus.
  - Associated with Turner syndrome
- \* Adult type or postductal:
- ✓ Stenosis is **d**istal to ligamentum arteriousm, associated with <u>notching of the rib</u> (due to
  - Hypertension in upper extremities and weak pulses in lower extremities

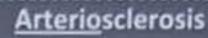
# Patent Ductus Arteriosus (PDA)

- The ductus arteriosus is a normal fetal artery connecting the aorta and the pulmonary artery. The ductus allows blood to detour away from the lungs before birth.
- Every baby is born with a ductus arteriosus. After birth, the opening is no longer needed and it
- usually narrows and closes by the end of the first month after birth. Sometimes, the ductus doesn't close after birth. Patent ductus arteriosus (PDA) is a persistent
- Machine-like murmur or Continuous murmur: This means that murmur occurs both during systole and during diastole. Best heard at the left Infraclavicular area
- PDA which is left (aorta) to right (pulmonary artery) shunt
- It is associated with congenital rubella. Loudest 52
- It is the most common anomaly of premature birth.
- What is shunt? when blood from the left side or right side of the heart mixed pathologically that
- What is left to right shunt? Left to right shunt means mixing of oxygenated blood with the nonoxygenated blood

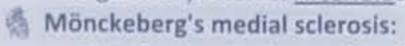
# Naseem Sherzad High-Yield Points

- Atrial septal defect (ASD): It is the most common congenital heart defect in adult, Ostium secundum defect is the most common form of ASD.
- ❖ Ventricular septal defect (VSD): it is the most common congenital heart defect in infancy and it is associated with fetal alcohol syndrome.
- TOF is the most common cyanotic heart disease which is compatible with life
- TOF is the most common cyanotic congenital anomaly observed in the adult.
- Transposition of the great arteries (TGA) is the commonest Cyanotic heart disease in first week of life (neonatal period)
- TOF and Persistent truncus arteriosus (PTA) are associated with DiGeorge syndrome





Arteriosclerosis is the general term reflecting arterial wall thickening and loss of elasticity and occurs in three general patterns: Arteriolosclerosis, Mönckeberg's medial sclerosis and atherosclerosis.



Chapter 4

- " Calcification in the media of the arteries (obstruction do not occur) especially in radial and ulnar.
- Usually benign, "pipestem" arteries
- Arteriolosclerosis: Hardening of small arteries and arterioles
  - Hyaline: Due to increase deposition of protein in the kidney, associated with DM and essential Hypertension
  - \* Hyperplastic: Due to smooth muscle cell hyperplasia in the kidney and associated with malignant hypertension. Concentrated, laminated and onion skin appearance

# Atherosclerosis

- · Key processes in atherosclerosis are intimal thickening & lipid accumulation means fibrous plaques and atheromas form in the intima of arteries and cause obstruction.
- Fatty streaks are the earliest lesions in atherosclerosis
- Foam cell in atherosclerosis is actually macrophage
- Common site: on decreasing order AC-PIC
  - ✓ Abdominal aorta posterior wall (most common)
  - √ Coronary artery
  - √ Popliteal artery
  - ✓ Internal carotid artery

# Risk factors for atherosclerosis:

- 1) Modifiable:
  - > Major:
    - Hypertension (systolic and diastolic)
    - ✓ Cigarette smoking
    - √ Diabetes
    - ✓ Hyperlipidemia---increased LDL and decreased HDL
  - > Minor:
    - ✓ Alcohol
    - ✓ Lipoprotein LP (a)
    - ✓ An infection like herpes virus, CMV and Chlamydia pneumonia.
- 2) Non-modifiable:
  - > Major:
    - √ Increased age
    - ✓ Male gender
    - Family history and Genetic alteration
  - > Minor:
    - √ Obesity
    - Physical inactivity
    - Stress (type-1 personality)
    - High carbohydrate intake and postmenopausal estrogen deficiency

# Cardiovascular System

THE RESIDENCE THE PARTY NAMED IN

rest

variant:

coronary

and

Prinzmetal's variant

Prinzmetal's

occur at

artery spasm

secondary to

ST-elevation on ECG

# Chapter 4

# Aneurysm

-----Popliteal artery

- The Commonest location of aneurysm in thoracic aorta———Ascending aorta Commonest peripheral vessels aneurysm--
- The Commonest location of Visceral artery aneurysm-----Splenic artery
- The Most common location for AAA----

# Abdominal Aortic Aneurysm

- It is by far the most common type of large vessels aneurysm, 95% have associated atheromatous degeneration, 95% occur below renal arteries
- Patient present with central abdominal pain and pulsatile mass (L1, L3 level)
- The two most important causes of aortic aneurysms are atherosclerosis and cystic
- Mycotic aneurysm, the term "Mycotic" is misnomer because; although it indicates infection as the cause of aneurysm, it is due to bacteria, not fungi.

# **Aortic Dissection**

- It present with inter-scapular pain (when descending aorta involve) and anterior chest pain (when ascending aorta involve) onset of which is sudden, severe in nature and
  - Hypertension and Marfan syndrome are the main risk factor (no association with atherosclerosis).
  - Chest X-ray (CXR) shows widened mediastinum.

# Angina

# Stable Angina Stable angina relieved by rest and nitrate and aggravated by physical exertion, heavy meals, cold exposures and intense emotion, it is secondary to atherosclerosis ST depression on ECG

NAME AND ADDRESS OF THE OWNER, WHEN

# Unstable/crescendo Angina

# It is defined as new onset angina or rapidly worsening angina or angina occurring at rest and is due to thrombosis with incomplete coronary artery occlusion

- ST depression on ECG.
- Negative cardiac enzymes

# Anti-anginal therapy

- Nitrates: cause venous and arterial dilation, decrease both preload and afterload---side effect headache and orthostatic hypotension
- Beta-blocker—these agent block sympathetic stimulation and lower myocardial oxygen demand
- CCB: these agents cause coronary vasodilatation and afterload reduction
- Potassium channel blocker

Cardiovascular System

# 1) Ist degree:

Chapter 4

- It is AV-block in which PR-interval is prolonged
- Causes: AV nodal disease, increase vagal tone like in athletes, acute inferior myocardial infarction

# 2) 2<sup>nd</sup> degree:

- Mobitz type I:
  - ✓ Also known as "wenckebach's phenomenon"
  - ✓ It is Characterized by progressive lengthening of PR-interval until a dropped beat occurs, and the cycle is repeated
- Mobitz type II:
  - ✓ It is characterized by a dropped beat without progressive lengthening of PRinterval
  - ✓ Atrial rate (75bpm) is greater than the ventricular rate (38bpm)
  - Conduction ratio (p-wave to QRS complex) is commonly 2:1, 3:1, 4:1
  - ✓ Atria regular and ventricular irregular

# 3) 3rd degree

- It is characterized interruption of AV-node conduction in which P-wave has no relation with QRS complex
- Pacemaker for complete heart block, Terminals should be in the right ventricle
- Clinical features:
  - ✓ Syncope and dizziness because of prolong period during which ventricle fails to contract
  - ✓ Cannon A-wave
  - ✓ Strokes Adam attack
- 4) Bifascicular block: Bifascicular block is the combination of RBBB with LAFB or LFFB, the ECG will show typical features of RBBB plus either left or right axis deviation, the most common cause of Bifascicular block is ischemic heart disease
- 5) Trifascicular block: Trifascicular block is the combination of heart block with a Bifascicular block and can be complete or incomplete. ECG has Prolong PR interval and left axis deviation

# **Atrial Fibrillation**



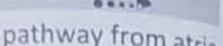
- Raised JVP without "a" wave
- Irregularly irregular pulse
- ECG: No P-wave, Irregularly irregular PR interval
- Pulses deficit
- Atrial fibrillation leads to the formation of the embolus

# **Atrial Flutter**



- It is characterized by single irritable atomicity focus (large re-entry cycle)
- Firing-rate---200-350 time/min
- ECG: regular rhythm, Saw-toothed appearance
- Best seen in II, III and avf

# WPW syndrome



- It is characterized by premature excitation of the ventricle due to an accessory pathway from atria known as "Bundle of Kint"
- ECG show: WPW
  - ✓ Wide QRS complex
  - Shortened PR-interval
  - Delta Wave I.e. slurring of QRS complex

# Marfan syndrome



- This condition is Inherited in an Autosomal dominant Multisystem disorder
- Marfan's syndrome is caused by the misfolding of fibrillin-1.
- Chromosome 15 are mutated
- Marfan syndrome is the risk factor for aortic dissection, mitral valve Prolapse and spontaneous Pneumothorax.
- Skeletal abnormalities are the most obvious feature of Marfan syndrome
- Patients have a slender, elongated habitus with abnormally long legs, arms, and fingers (arachnodactyly); a high-arched palate; and hyperextensibility of joints.
- The most characteristic ocular change is bilateral dislocation, or subluxation, of the lens owing to the weakness of its suspensory ligaments
- Most serious, however, is the involvement of the cardiovascular system. Fragmentation of the elastic fibers in the tunica media of the aorta predisposes to aneurysmal dilation and aortic dissection
- Death from aortic rupture may occur at any age and is the most common cause of death. Less commonly, cardiac failure is the terminal event.

### **Acute Pericarditis**



- Chest pain is typically aggravated by deep breathing, moment and change of position
- Pericardial friction rub: it is diagnostic of Pericarditis, usually heart in systole
- ECG: it's diagnostic, it shows widespread ST-elevation with upward concavity and PR-interval depression
- Type of pericarditis in acute renal failure is Fibrinous pericarditis



# Cardiomyopathy



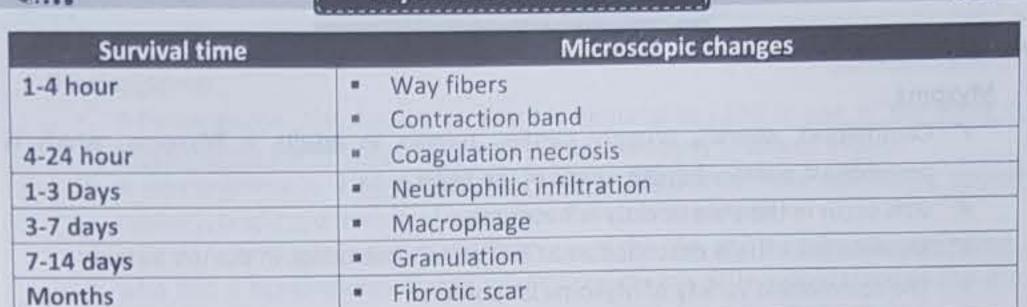
- Selenium deficiency can cause hypothyroidism, cardiomyopathy in children (Keshan's disease) and myopathy in the adult. Excess selenium can cause heart disease
- The most common type of cardiomyopathy is dilated (congestive) cardiomyopathy.
- Hypertrophic cardiomyopathy is the most common cause of sudden cardiac death in young people. It is due to an autosomal dominant mutation in the cardiac sarcomere gene, 50% cases are sporadic. It is characterized by myocardial fiber disarray with hypertrophy

Chapter 4

# NASEEM SHERZAD FCPS -1 HIGH-YILLD

Cardiovascular System

# Myocardial infarction

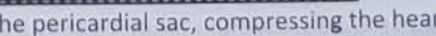


Area of infarction	Leads	Artery involved
Inferior wall MI	II, III, aVF	Right marginal artery -CPSP
Anterior wall MI	V3 and V4	LAD
Anterior-septal wall MI	V1, V2, V3 & V4	LAD
Lateral wall MI	I, aVL, V5, V6	Left anterior descending or circumflex

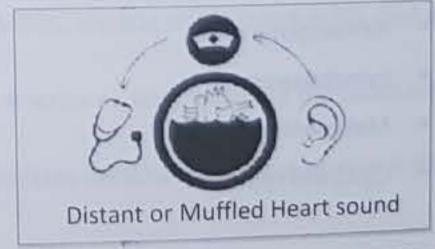
# Naseem Sherzad High-Yield Points

- Infarct are most frequently located in the left ventricle
- The right ventricle is less susceptible to infarction due to its thin wall, having less metabolic requirement and is thus adequately nourished by thebesian vessels
- Atrial infarct, whenever present, are more often in the right atrium, usually accompanying the infarct of the left ventricle
- The left atrium is relatively protected from infarction because it is supplied by the oxygenated blood in the left atrial chamber.
- The most common coronary artery involves in myocardial infarction is left anterior descending artery (LAD).
- The most common cause of right heart failure is the left heart failure.
- Chest pain less than 30min in angina and greater than 30 min in MI
- . Chest pain relieved by nitrates and rest in angina, but no so in MI
- \* Dressler's syndrome: Autoimmune phenomena resulting in Fibrinous pericarditis 2-10 weeks post-MI---clinical features: fever, pericarditis and pleurisy
- Ventricular free wall rupture is the most common mechanical complication following MI and it present as cardiac tamponade and is usually fatal. Free-wall rupture may occur at almost any time after MI but is most frequent 3 to 7 days after onset.

# **Pericardial Tamponade**



- It is due to collection of fluid in the pericardial sac, compressing the heart
- Clinical features:
  - √ Beck's triad: 3-D's
    - Distended Jugular veins,
    - o Decreased arterial pressure
    - o Distant or muffled heart sound
  - √ Kussmaul's sign
  - ✓ Pulsus paradoxicus



# **TUMORS OF HEART**



# (1) Primary Tumors:

#### Myxoma:

- ✓ Commonest, overall, primary cardiac tumors in adults is Myxoma, which is the commonest primary benign tumor of the heart.
- √ 90% occur in the atria (mostly left atrium)
- ✓ Myxoma are usually described as a "ball valve" obstruction in the left atrium
- ✓ The commonest variety of Myxoma is sporadic
- √ Stellate shaped cells present

#### Rhabdomyoma

- ✓ It is the Most common primary cardiac tumor in infants and children
- ✓ it is benign
- ✓ the most common site is ventricles.
- ✓ It is associated with tuberous sclerosis.
- ✓ There is a defect is TSC1 and TSC2 tumor suppressor genes.
- ✓ Microscopically there are spider cells (Stellate shaped cells )
- Angiosarcoma: Most common primary malignancy of the heart in the adult is Angiosarcoma
- Fibroma
- Lipomas (LV is common site)
- Papillary fibroelastomas: This is the commonest tumor of cardia valve. It has sea anemone like lesions i.e. there is a core of myxoid tissue which is surrounded by concentric elastic fibers )
- Extracardiac tumors: found at the base of the heart. Includes aortic body tumors and ectopic endocrine tumors e.g. thyroid and parathyroid

# (2) Secondary (Metastatic tumors)

The most common heart tumor is metastasis, the most common site is pericardium of heart, most common route retrograde lymphatic extension and the most metastatic tumors to the heart is lung carcinoma. Tumors' are;

- Lung carcinoma(commonest)
- · Renal cell carcinoma can extend into the right atrium
- Breast carcinoma
- Hamangiosarcoma
- Lymphosarcoma
- Malignant melanoma
- Carcinoid tumor

## Vascular Tumors

## a) Benign:

Chapter 4

### Hemangioma:

- ✓ A hemangioma, also known as infantile hemangioma (IH) is one of the most common benign tumors of infancy and occurs in approximately 5-10% of infants.
- ✓ A hemangioma is a <u>birthmark (port-wine stain</u>) that most commonly appears as a rubbery, bright red nodule of extra blood vessels in the skin.
- ✓ A hemangioma grows during the first year of the life, and then recedes over time. A child who had a hemangioma during infancy usually has little visible trace of the growth by age 10.
- Lobular capillary hemangioma (Pyogenic granuloma) is a common oral benign tumor occurring as Polypoidal form attached to the mucosa
- Hemangioma are of three types
  - o Capillary hemangioma,
  - Cavernous hemangioma
  - Pyogenic granuloma (lobular capillary hemangioma)
- Lymphangioma Which is divided into
  - ✓ Simple (capillary) Lymphangioma, and
  - √ Cavernous Lymphangioma(cystic hygroma)
- Glomus tumors(Glomangioma):
  - ✓ seen mainly in fingers
  - They are often painful, and the pain is reproduced when the lesion is placed in cold water

# b) Intermediate Tumors:

- Hemangioma endotheliuma (hemangiondothelioma)
- Hemangioma pericytoma (Hemangiopericytoma)
- Kaposi Sarcoma: it is divided into chronic KS (classic or European type), lymphadenopathic KS (African or endemic type) and transplant associated KS

# c) Malignant

- Angiosarcoma
- Malignant Hemangiopericytoma

# d) Fibromuscular dysplasia (FMD)

- Fibromuscular dysplasia (FMD) is an angiopathy that affects medium-sized arteries predominantly in young women of childbearing age.
- Among patients with identified FMD, renal involvement occurs in 60-75% (renal artery, 35%) bilateral), cerebrovascular involvement in 25-30%, visceral involvement in 9%, and arteries of the limbs in about 5%.
- FMD occurs in most other medium-to-large arteries as well, including the coronary arteries, the pulmonary arteries, and the aorta.
- FMD is different from most other vascular diseases because it does not involve inflammation or plaque.

Cardiovascular System

# Chapter 4

# Cardiac Markers

- Cardiac enzymes are marker found in the blood
- They are tested when myocardial infarction (heart attack) is suspected
- The marker are presents at all time, they are significantly elevated during a damage of the heart muscles
  - i. Troponin: Contractile protein, two types
    - a) Troponin T (TnT):
    - b) Troponin I (Tnl):
      - Time of initial elevation = 4-6 hour
      - Time of peak elevation= 12 hour
      - Time to return to normal= 3-10 days
      - Troponin I is more specific than Troponin T
      - Troponin-I has the highest sensitivity and specificity

### ii. Creatine phosphokinase (CK-MB)

- Time of initial elevation = 4-8 hour
- Time of peak elevation= 12-24 hour
- Time to return to normal= 72-96 hour
- It is useful in diagnosing reinfarction following acute MI

#### iii. LDH

- LDH is called lazy enzyme, because it comes late and goes late
- Time of initial elevation =6-12 hour
- Time of peak elevation= 24-48 hour
- Time to return to normal= 6-8 days
- LDH and CK-MB can be found together on 2<sup>nd</sup> day.

#### iv. Myoglobin:

- Myoglobin first come and first goes (first rises, first disappear)
- Myoglobin is a muscle protein with <u>high sensitivity</u>, but low specificity
- . Time of initial elevation = 2-4 hour
- Time of peak elevation= 8-10 hour
- Time to return to normal= 24 hour
- v. Note: A Myoglobin blood test may be used detect muscle damage. When heart or skeletal muscle is injured, myoglobin is released into the blood. Blood levels of myoglobin can rise very quickly with severe muscle damage and can be measured within a few hours following an injury
- Summary: Troponin is the best overall markers, they have the best combination of sensitivity, specificity and easy of performance of all the markers. CK-MB is the second best, the first marker to go up in myocardial infarction is Myoglobin but it's not good test to use for ruling in MI. Troponin I and T and are not enzyme but protein.

# Chapter 4

Cardiovascular System

# Libman-Sacks Endocarditis

Endocarditis of Systemic Lupus Erythematosus (Libman-Sacks Disease): In SLE, mitral and tricuspid valvulitis with small, sterile vegetations, called Libman-Sacks endocarditis is occasionally encountered.

- Commonest side of mitral valve involved in Libman sacks syndrome———Atrial side
- Commonest combination of valve involved in Libman sack syndrome is----- Mitral and aortic
- Commonest abnormality in Libman sack syndrome------Regurgitation
- Nonbacterial Thrombotic Endocarditis (NBTE)
  - ✓ NBTE frequently occurs concomitantly with venous thromboses or pulmonary embolism, suggesting a common origin in a hypercoagulable state with systemic activation of blood coagulation such as disseminated intravascular coagulation.
  - ✓ This may be related to some underlying disease, such as a cancer, and, in particular, mucinous adenocarcinomas of the pancreas.
  - ✓ NBTE is often encountered in debilitated patients, such as those with cancer or sepsis-hence the previously used term marantic endocarditis.

# Naseem Sherzad High-yield Points

Temporal arteritis (Giant cell arteritis)		Polyarteritis nodosa (PAN)	Takayasu arteritis	
	laudication & la	<ul> <li>It involves all the system but spares Lung (pulmonary artery)</li> <li>it is associated with Hepatitis B and there is Transmural inflammation of arterial wall with fibrinoid necrosis</li> </ul>	and hypertension, granulomatous thickening	

# Heart failure cells:

- · Sidrophages-----Hemosiderin containing Macrophage
- · Which is generated in the alveoli of the patient with left heart failure or chronic pulmonary edema

# Mitral valve Prolapse (MVP):

- Also known as "Barlow syndrome" or "floppy mitral valve"
- · Occur due to Myxomatous degeneration of the mitral valve.
- . Buerger's disease or Thromboangiitis obliterans is related to smoking
- Churg-strauss syndrome -AGE-- = Asthma + Granulomatous vasculitis+ Eosinophilia.
- Essential or idiopathic hypertension is the most common and accounts for 95 % cause of hypertension.
- Artificial arterializations of the ventricle is seen in Ebstein anomaly
- \* BNP can differentiate dyspnea of cardiac origin from the respiratory origin
- Type A Personality can develop cardiac problem due to the stress of the social environment
- During cardiac imaging phase of the minimum motion of heart can be seen in mid-diastolic

# Anti-Arrhythmics

#### β-Blockers-----Class-II Na+ channel blockers----Class 1 LOL Metoprolol . Class IA: ✓ Quinidine, procainamide, Propranolol Esmolol: Esmolol is a cardioselective disopyramide beta-1 receptor blocker with rapid ✓ Mnemonics: "the Queen Proclaims onset, a very short duration of action, Diso's pyramid significant intrinsic . Class 1B: and ✓ Lidocaine, Mexiletine, Tocainide membrane-Sympathomimetic therapeutic stabilizing activity . Class IC: √ Flecainide, Propafenone dosages. ✓ Class IC is Contraindicated in structural. Atenolol heart disease and post-MI \* Timolol

# K+ Channel Blocker----Class-III

- Mnemonic———AIDS
- Amiodarone, Ibutilide, Dofetilide, Sotalol
- Amiodarone
  - ✓ Wide spectrum anti-arrhythmic drugs
  - ✓ has class I, II, III, IV effects because it alters the lipid membranes
  - ✓ the first line drugs for stable ventricular tachycardia (VT)
  - ✓ Side effects:
    - o Hypotension
    - Pulmonary fibrosis
    - o Hypo/hyperthyroidism
    - Hepatic granuloma

# Ca2+ Channel Blocker----Class-IV

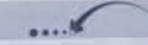
· Verapamil, Diltiazem

# Other Anti-arrhythmics

- \* Adenosine:
  - MOA: increase K+ out of cells
  - ✓ DOC in: diagnosing/abolishing SVT
  - ✓ Very short-acting (15 sec)
  - ✓ Effects blocked by caffeine and Theophylline

# C H A P T E R

# HEAD AND NECK



- Skull has 22 bones excluding the ossicles of the ear
- In the infant, the bones of the skull are more resilient than in the adult, and for this reason fracture of the skull are much more common in the adult than in the young child.
- Paired bone-----Temporal, Parietal, Nasal Bones, Palatine Bones, Lacrimal Bones, Zygomatic Bones, Maxillae, Inferior Nasal Conchae
- Unpaired------ Frontal, Sphenoid, Ethmoid, Occipital Bones And Vomer
- The nasal bone is the most common facial bone to be fractured followed by Zygomatic.
- The zygomatic bone (cheekbone or malar bone) is a paired bone, which articulates with the maxilla, the temporal bone, the sphenoid bone and the frontal bone.
- The single frontal bone forms the Forehead
- Inion is the most prominent projection of the protuberance, which is located at the posterioinferior (lower rear) part of the human skull.
- Pneumatic bone are irregular bone containing large airspaces lined by epithelium e.g. Sphenoid, Ethmoid, Maxilla and mastoid
- Mastoid process of the temporal bone is absent at birth
- The Thinnest orbital wall is the medial wall
- Battle's sign is primarily caused by a type of serious head injury called a basilar skull fracture, or basal fracture.
- · Glabella, The area between the eyebrows, just above the nose or frontal bone between super ciliary arches
- Vault is bigger than the face in children
- Parts of 7 bone contributes in the bony framework of each orbit of the eye
- Calvaria: The Calvaria is the top of the skull. It is the upper part of the neurocranium and covers the cranial cavity containing the brain.
- Sutures visible internally include:
  - ✓ The coronal suture, between the frontal and parietal bones;
  - ✓ The sagittal suture, between the paired parietal bones;
  - ✓ The lambdoid suture, between the parietal and occipital bones
  - The metopic suture or frontal suture is noted to be between the two frontal bones extending from the nasion to the bregma. The metopic suture generally fuses between 1 and 8 years of life. In some adults, the separation line persists as the metopic suture in the midline of the glabella, the smooth, slightly depressed area between the superciliary arches.

# Chapter 5

# Fontanelle

- It is diamond-shaped and lies between the two halves of the frontal bone and two Parietal Anterior Fontanelle (Bregma):
- Heart rate, intracranial pressure and degree of dehydration can be examined by palpating the
- anterior fontanelle. Anterior is larger than posterior

# Posterior Fontanelle (Lambda)

- It is triangular in shape, lies between the two parietal bone and occipital bone
- It is usually closed by the end of the first year

# **Dural Partitions**

# Falx cerebri:

■ The falx cerebri is a crescent-shaped structure that projects downward between the two cerebral hemispheres from the dura covering the calva. It is attached anteriorly to the crista galli of the ethmoid bone and frontal crest of the frontal bone. Posteriorly it is attached to and blends with the tentorium cerebelli.

# Tentorium cerebelli

The tentorium cerebelli is a horizontal projection of the meningeal dura mater that covers and separates the cerebellum in the posterior cranial fossa from the posterior parts of the cerebral hemispheres

# Falx cerebelli:

The falx cerebelli is a small midline projection of meningeal dura mater in the posterior cranial fossa. It is attached posteriorly to the internal occipital crest of the occipital bone and superiorly to the tentorium cerebelli. Its anterior edge is free and is between the two cerebellar hemispheres.

# Diaphragma sellae

 The final dural projection is the diaphragma sellae. This small horizontal shelf of meningeal dura mater covers the hypophysial fossa in the sella turcica of the sphenoid bone

# Scalp

# Layers: SCALP

- ----- Skin, contain hair-----first layer
- C----- Connective tissue (dense), connect the skin to the epicranial aponeurosis Contains the arteries, veins, and nerves supplying the scalp, 2nd layer
- A------Aponeurotic layer, contain occipitofrontalis muscle (supplied by branches of facial nerve-The frontal branch of the facial nerve supplies the frontal bellies of the occipitofrontalis muscle, and the auricular branch of the facial nerve supplies the occipital bellies of the muscle)-----3rd layer
- I-----loose Areolar connective tissue---contain emissary's vein, that's why it's the danger area—blackening of the eye, infection of scalp spread through this layer, 4th layer
- p-----Pericranium-----5<sup>th</sup> layer

# Nerve supply: GLASS

Chapter 5

- Greater occipital/ Greater auricular
- Lesser occipital
- Auriculotemporal---supply temporal scalp
- Supratrochlear-----supplies the anteromedial forehead.
- Supraorbital---supplies a large portion of the scalp between the anterolateral forehead and the vertex.

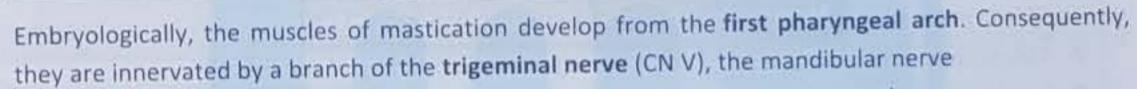
# Blood supply:

- Superficial temporal artery supplies the frontal and temporal regions
- Posterior auricular artery supplies the area superiorly and posteriorly to the auricle.
- Occipital artery supplies the back of the scalp
- Ophthalmic artery: supplies the anterior and superior regions of the scalp

# Lymph drainage of the skull:

- Lymph vessels in the anterior part of the scalp and forehead drain into the submandibular lymph nodes
- Drainage from the lateral part of the scalp above the ear is into the superficial parotid (preauricular) nodes; lymph vessels in the part of the scalp above and behind the ear drain into the mastoid nodes. Vessels in the back of the scalp drain into the occipital nodes.

# Muscle of Mastication



- Medial pterygoid muscle------Elevates the mandible, closing the mouth.
- Masseter muscle: The Masseter muscle is the most powerful muscle of mastication. The hallmark of a masticatory space infection is trismus. The cardinal signs of this infection include a firm mass in the body of the Masseter muscle with overlying cellulitis and trismus.

# Lateral pterygoid muscle:

- The lateral pterygoid muscle cause protrusion of the mandible
- Lateral pterygoid is mostly damaged during TMJ dislocation
- The lower head of lateral pterygoid enters between both heads of the medial pterygoid muscle.
- It is the only masticatory muscle, which opens the mouth.
- The articular disc of Temporomandibular joint is developmentally a part of the tendon of the lateral pterygoid muscle.
- The pterygoid venous plexus is occasionally known as a peripheral <u>heart</u>, during yawning when the mouth is broadly open because of the contraction of the lateral pterygoid muscle.

# Temporalis muscle:

- It arises from the temporal fossa and the deep part of temporal fascia. It passes medial to the zygomatic arch and forms a tendon which inserts onto the coronoid process of the mandible
- Actions: Elevates the mandible, closing the mouth. Also retracts the mandible, pulling the jaw posteriorly.

# Temporomandibular Joint (TMJ)

# Introduction:

- TMJ is a modified hinge type synovial joint
- Fibrocartilage divided the joint into upper and lower cavities
- The capsule encloses the joint

# Ligaments:

- Stylomandibular ligament:
  - ✓ Formed by deep part of the parotid fascia
- Sphenomandibular ligament:
  - ✓ It is derivatives of 1st arch
- Lateral ligament or Temporomandibular ligament
  - ✓ The thick part of the articular capsule forms the intrinsic lateral ligament (Temporomandibular ligament) which strengthens the TMJ laterally.
  - ✓ Act to Prevent posterior dislocation of the joint

# Nerve supply:

- Auriculotemporal nerve—Sensory supply of capsule of TMJ
- Masseter nerve

# Blood supply:

Superficial temporal artery

# Naseem Sherzad High-Yield Points

- \* TMJ dislocation most commonly occur during extreme opening of the mouth
- · Sudden contraction of lateral pterygoid muscle as in yawing, may be sufficient to pull the disc forward beyond the summit and dislocation occurs.
- \* Except for the Geniohyoid muscle, which is innervated by the C1 spinal nerve, all muscles that move the Temporomandibular joints are innervated by the mandibular nerve by branches that originate in the infratemporal fossa.
- TMJ dislocation occurs when the condyle of the jaw moves forward, out of its functional position within the glenoid fossa and posterior articular eminence so that the condyle is anterior to the eminence

## Mandible

- . The mandible is the largest and strongest bone of the face
- . The Mandible is the second bone after clavicle to ossify in the body
- . Each half of mandible ossifies from one center, which appears in the 6th week of intrauterine life in the mesenchymal sheath of Meckel's cartilage. Two types of ossification seen in the mandible

# Mental foramen:

- ✓ The mental foramen can be seen below the 2<sup>nd</sup> premolar teeth
- ✓ Transmit the mental nerve and vessels.
- ✓ Pressure on the mental nerve can cause numbness of the lower lip
- Mandibular foramen:

- ✓ Inferior alveolar nerve and vessels enter the mandibular canal through this mandibular foramen
- ✓ Inferior alveolar nerve supplies all lower jaw teeth, lower lips, Buccal mucosa from the incisor to the premolar and the skin over the chin

# Mandibular canal:

- ✓ It contains the inferior alveolar nerve, inferior alveolar artery, and inferior alveolar vein.
- ✓ It is continuous with the mental foramen (which opens the front of mandible) and mandibular foramen (on the medial aspect of ramus)

# Mylohyoid groove:

Mylohyoid nerve and vessels lie in this groove

## Mandibular fracture:

- Mandibular fractures are typically the result of trauma
- The most common area of the fracture is at the condyle (36%), body (21%), angle (20%) and Symphysis (14%)
- ✓ Mandibular fracture just before the mandibular foramen will cause loss of sensation of lower jaw teeth and lower lip due to damage to inferior alveolar nerve

# **Key Neck Muscles**

# Sternocleidomastoid Muscle:

- ✓ Origin: Manubrium and medial third of clavicle
- ✓ Insertion: mastoid process
- ✓ Action: Rotate head to opposite side, extend head and flex vertebral column
- ✓ Nerve Supply: Spinal part of accessory nerve
- ✓ Damage to Sternocleidomastoid muscle will cause difficulty in turning the neck to the opposite side against resistance
- ✓ It forms a prominent landmark surface in the neck
- ✓ EJV run perpendicular to SCM

# Platysma

✓ Nerve Supply: Cervical branch of Facial nerve

# Suprahyoid muscles:

- Digastric
  - ✓ Nerve Supply: Posterior belly: Facial nerve Anterior belly: Nerve to Mylohyoid
  - Between the two bellies of the digastric, intermediate tendon is attached to the hyoid bone
- Stylohyoid
  - ✓ Nerve Supply: Facial nerve
- Mylohyoid

- ✓ Nerve Supply: Inferior alveolar nerve
- Geniohyoid
  - ✓ Nerve Supply: First cervical nerve
- Infrahyoid muscles:
  - \* Sternohyoid
    - ✓ Nerve Supply: Ansa cervicalis; C1, 2, and 3
  - Sternothyroid
    - ✓ Nerve Supply: Ansa cervicalis; C1, 2, and 3
  - Thyrohyoid
    - ✓ Nerve Supply: First cervical nerve
  - \* Omohyoid
    - Nerve Supply: Ansa cervicalis; C1, 2, and 3



# Triangle of Neck

For description, neck is divided into anterior and posterior triangle by Sternocleidomastoid muscle

# Anterior Triangle

- Cover: investing fascia
- Floor: visceral fascia
- The Sensation of the anterior triangle is mediated through: C2, C3
- Muscular triangle: (Paired)
  - Boundaries
    - √ Superiorly: hyoid bone
    - ✓ Medially: imaginary midline
    - ✓ Laterally: Superiorly by Superior belly of Omohyoid muscle and inferiorly by SCM
  - Contents:
    - ✓ Pharynx, thyroid, parathyroid and infrahyoid muscle, covered by pretracheal layer.
- Submandibular triangle/Digastric triangle: (Paired)
  - Boundaries:
    - ✓ Superiorly: the body of the mandible.
    - ✓ Anteriorly: the anterior belly of the digastric muscle
    - ✓ Posteriorly: the posterior belly of the digastric muscle.
  - Contents:
    - ✓ Submandibular gland and facial artery
- Carotid triangle: (Paired)
  - Boundaries
    - ✓ Superiorly: posterior belly of digastric muscle.
    - ✓ Laterally: medial border of SCM
    - ✓ Inferiorly: superior belly of Omohyoid muscle.

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- ✓ Common carotid artery, IJV, vagus nerve and hypoglossal nerve
- Submental triangle: (Unpaired)
  - Boundaries: IMAL
    - ✓ Inferiorly: hyoid bone
    - ✓ Medially: midline
    - ✓ Laterally: anterior belly of digastrics muscle
  - \* Contents:
    - ✓ Submental lymph node

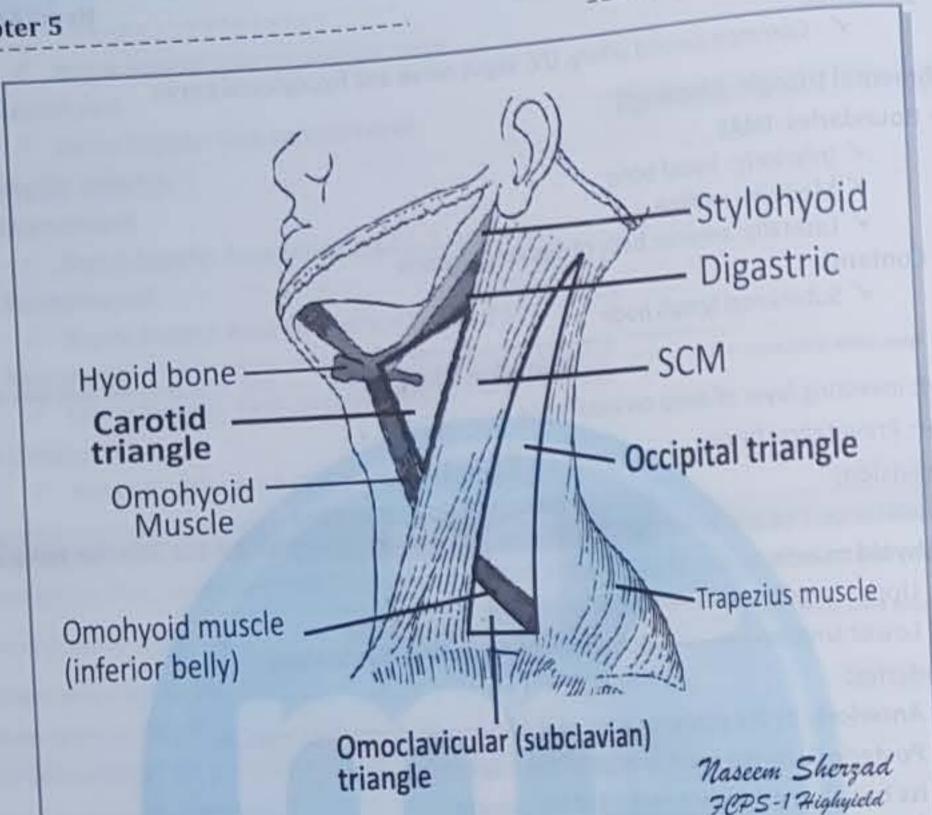
## Posterior Triangle

- Roof: investing layer of deep cervical fascia
- Floor: Prevetebral fascia
- Subdivision:

The posterior triangle is further divided into two smaller triangles by the inferior belly of the Omohyoid muscle

- ✓ Upper larger part-----Occipital triangle
- ✓ Lower smaller———Subclavian or supraclavicular triangle
- Boundaries:
  - ✓ Anteriorly by the posterior edge of the Sternocleidomastoid muscle
  - Posteriorly by the anterior edge of the trapezius muscle
  - ✓ Its base is the middle one-third of the clavicle
  - ✓ Its apex is the occipital bone just posterior to the mastoid process where the attachments of the trapezius and Sternocleidomastoid come together.
- Contents:
  - ✓ External jugular vein:
    - One of the most superficial structures passing through the posterior triangle of the neck is the external jugular vein
  - ✓ Spinal part of accessory nerve:
    - o The superficial location of the accessory nerve as it crosses the posterior triangle makes it susceptible to injury.
  - √ 3<sup>rd</sup> part of the subclavian artery:
    - The largest is the third part of the subclavian artery as it crosses the base of the posterior triangle
    - O A single branch (the dorsal scapular artery) may arise from the third part of the subclavian artery
  - ✓ Brachial plexus:
    - The trunks cross the base of the posterior triangle
  - Cervical plexus:
    - The cervical plexus is formed by the anterior rami of cervical nerves C2 to C4, and possibly a contribution from the anterior ramus of cervical nerve C1
  - Transverse cervical and Suprascapular arteries also cross the base of the posterior triangle
  - Muscle: inferior belly of Omohyoid muscle

Head And Neck



Ear

- The average length of the external auditory canal in the adult is 2.5 cm or 1 inch whereas the average length of the Eustachian tube is 36 mm.
- External auditory meatus: The outer-third has a framework of elastic cartilage and the inner twothird have a framework of bone. It develops from (ectodermal) first pharyngeal cleft
- Auditory tube: Posterior one third is bony and the anterior two third are cartilaginous. The tensor veli palatini muscle acts as the primary dilator of the Eustachian tube and may aerate the middle ear to prevent recurrent Otitis media and hearing loss.
- Tympanic reflex: The tympanic reflex helps prevent damage to the inner ear by muffling the transmission of vibrations from the tympanic membrane to the oval window. The reflex has a response time of 40 milliseconds, not fast enough to protect the ear from sudden loud noises such as an explosion or gunshot.
- Endolymph contains a high amount of potassium, also remember that tear has the highest concentration of Na\*
- Nystagmus is caused by endolymph in the semicircular canal
- Benign paroxysmal positional vertigo(BPPV): Dix-Hallpike/Barany maneuver along with typical patient history—diagnostic for BPPV
- Alternobaric vertigo: Failure to equalize the pressure of the inner ear on the ascent

#### Otosclerosis:

#### √ Paracusis willisii:

o This occurs in an otosclerotic patient who hears better in the noisy environment than in quiet surroundings because normal person will raise his voice in noisy surroundings.

### **Embryology of Ear**

- The auricle (pinna) develops from mesenchymal proliferation in the first and second pharyngeal arches
- External and inner ear develops from ectoderm
- Ear ossicles are almost of adult size at birth and develops from first and 2<sup>nd</sup> pharyngeal arch
- Stapes develops from the cartilage of pharyngeal arch 2 (Reichert's cartilage).
- Malleus and incus develops from pharyngeal arch 1 (Meckel's cartilage)
- The epithelial lining of auditory tube and middle ear cavity develops from first pharyngeal pouch
- Embryonic origin of the Stapedial artery: it is the persistent artery of the 2<sup>nd</sup> branchial arch
- Tympanic membrane develop from all three germ layers

# Difference between Perilymph and Endolymph

Perilymph	Endolymph	
Resembles ECF	Resemble ICF	
<ul> <li>Present in scala tympani and scala vestibuli</li> </ul>	Present in scala media	
The Major cation isNa	■ The Major cation isK <sup>+</sup>	
<ul> <li>Has the potential of Omv</li> </ul>	Has the potential of 80mv	

# **Hearing loss**

### Conductive hearing loss:

- ✓ Rinne test: abnormal-----bone > air
- ✓ Weber test: localized to the affected ear

# Sensorineural hearing loss:

- ✓ Rinne test: Normal----air> bone
- Weber test: localized to unaffected ear
- Noise-induced: Damage to sterocilliated cell organ of Corti; loss of high-frequency hearing ist, sudden extremely loud noises can produce loss due to tympanic membrane rupture
- Human can hear best in frequency range of 1000-2000db

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# The Middle ear

- ✓ The Superior wall or Roof: A thin plate of bone called the Tegmen tympani forms the roof, it
- ✓ The Inferior wall or floor: Thin plate of bone which separates tympanic cavity from the jugular
- The Anterior wall: Thin plate of bone which separates the tympanic cavity from the internal carotid artery, and having two opening the upper one is for the canal of tensor tympani muscle
- The posterior wall: The aditus to the mastoid antrum below this is a hollow, conical projection from whose apex emerges the tendon of Stapedius muscle.
- The Lateral wall: Tympanic membrane
- The Medial wall: The lateral of the inner ear and is formed by the labyrinth
- Concentration of normal air in the middle ear: Nitrogen: 83%, oxygen: 9%, carbon dioxide 6%
- ✓ It Contains:
  - O Promontory: Rounded projection resulting from the underlying first coil of the cochlea
  - Oval window or the fenestra vestibule: Covered by the footplate of stapes.
  - Round window or the fenestra cochlea: covered by secondary tympanic membrane
  - Facial canal: Above the oval window is the canal for the facial nerve.

#### Inner ear

# Semicircular canal:

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- Respond to rotational (angular), nonlinear movement of the head (like playing on merry go round)
- Otolithic organ:
  - ✓ The Utricle is sensitive to Horizontal acceleration (like traveling in a car),
  - ✓ The Saccule is sensitive to <u>Vertical</u> acceleration (like moving in the elevator).

# **Referred Pain to Ear**

- Pain in acute tonsillitis is referred to the ear through: 9th nerve
- . Also Remember the nerve damage in tonsillectomy is: 9th nerve
- Pain in cancer larynx is referred to the ear through: 10th nerve
- Pain in cancer of pyriform fossa is referred to the ipsilateral ear via: 10th nerve
- Pain in Temporomandibular joint is referred to the ear through; 5th nerve
- Pain in salivary calculi is referred to the ear through: 5th nerve
- Pain in acute sinusitis is referred to the ear through: 5th nerve
- . The Pain of mumps is carried by greater auricular nerve
- Also, remember that Pain in Parotitis is due to stretching of the tough fibrous capsule while pain is transmitted via Auriculotemporal nerve caused by compression of the nerve

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**Head And Neck** 

# Nose

When furuncle or boil over the nose is squeezed or permanently incised, the infection can spread to cavernous sinus through venous Thrombophlebitis and cause fatal complication, cavernous sinus thrombosis.

- Ethmoid is the key area in the disease causation and acts as a reservoir of infection
- Histologically, Ethmoidal polyps are of two types' i-e neutrophil type and eosinophils type.
- The philtrum is formed where the nasomedial (or medial nasal process) and maxillary processes meet during embryonic development (colloquially known as Hulse lines). When these processes fail to fuse fully in humans, a cleft lip (sometimes called a "hare lip") can result. A flattened or smooth philtrum can be a symptom of Fetal alcohol syndrome or Prader-Willi syndrome.
- Most common artery involved in posterior nasal bleeding is the posterior ethmoidal artery
- CSF rhinorrhea:

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- ✓ Leakage of CSF into the nose is called CSF rhinorrhea.
- The most common site of the leak in CSF rhinorrhea is cribriform plate
- Beta-2 transferrin: protein seen in CSF and not in nasal discharge

# Main Features of the Lateral Wall of Nose Are

The lateral wall has three projections called the superior, middle and inferior conchae. The space below each is called a meatus:

Sphenoethmoidal Recess: it is a small area above superior conchae and it receive the opening of Sphenoidal air sinus

- Superior meatus: it lies below the superior conchae. It receives the opening of the posterior ethmoidal sinuses.
- Middle meatus: it lies below the middle conchae and is the most complex and by far the most important
  - Bulla ethmoidalis: it is a smooth rounded mass formed by the middle ethmoidal sinuses.
  - ✓ Hiatus semilunaris: it is a cured opening lies below and in front of the bulla and leads forward into the infundibulum. It is bounded below by the uncinate process of the ethmoid.
  - Maxillary air sinus: opens into the hiatus semilunaris below the bulla ethmoidalis.
  - Anterior ethmoidal sinus: opens into the hiatus semilunaris in front of the bulla ethmoidalis.
  - Middle ethmoidal sinus: opens on the bulla ethmoidalis.
  - Frontal sinus: opens into the upper part of the hiatus semilunaris.
- Inferior meatus receives the nasal opening of the Nasolacrimal duct which is partially covered by a mucosal fold (valve of Hasner or plica lacrimalis)
- Nasolacrimal duct is derived from endoderm
- Optic nerve is related to posterior ethmoidal sinus

# Three different Narrowest area in some part of the body

- Internal nasal valve
- External urethral meatus
- The Esophagus is narrowest at cricopharyngeous,
- Cricopharyngeous muscle also act as sphincter at the pharynx

Eye

# Epithelium

- Conjunctiva-----Stratified columnar epithelium
- Cornea-----Stratified squamous epithelium (noncornified)

# Embryology

Retina develop from the optic vesicle

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- Ciliary body develop from both Neuroectoderm and mesoderm
- Optic groove appears on the left side of forebrain on day 22

# Physiology

- The visual pigment of Rod is Rhodopsin (Opsin + 11-cis retinal)
- Visual impulse (light phase) cause breakdown of Rhodopsin into Opsin plus All-trans retinal
- During the dark phase all All-trans retinal converts to 11-cis retinal form, which combine with Opsin and regenerate Rhodopsin.
- The Power of the eye is 59 diopters. The main role in the maintenance of this power as performed by Anterior surface of the cornea
- Pretectem—light reflex or consensual light reflex
- The Visual cortex is the site of fusion of binocular vision
- Corneal reflex-----afferent= CN 5 (nasociliary nerve a branch of the ophthalmic nerve, one of the branch of CN 5 ) and efferent = CN 7
- The COVER test is used to confirm and detect Tropias, UNCOVER test is used for Phorias (or latent deviation), alternating cover test or cross cover test is used to detect total deviation (Tropias + Phorias)
- Retinoblastoma is the tumor of the retina that occurs in childhood and develops from precursor cells in the immature retina. The RB gene is located on chromosome 13 and encodes for RB protein. The Optic nerve is the most common route of spread
- The Basic mechanism involved in aqueous humour production is active sodium secretion
- Children with lacrimal duct obstruction, probing should be delayed till 12-18 months
- Bell's phenomenon (also known as the Palpebral oculogyric reflex) is a medical sign that allows observers to notice an upward and outward movement of the eye, when an attempt is made to close the eyes. The upward movement of the eye is present in the majority of the population, and is a defensive mechanism.

# Type of Color blindness

- -Red cones cell defective
- -Green cones cell defective Deuteranope----
- -Blue cones cell defective Tritanope --

## Horner's syndrome

- Results from an interruption of the sympathetic nerve supply to the eye and is characterized by the classic triad of: MAP
  - Miosis (i.e. constricted pupil), Pupilae dilator/ pupil radial muscle fibers paralysis leading to Miosis-- Parasympathetic predominance
    - Anhidrosis: Loss of hemifacial sweating
    - O Ptosis, Superior tarsal muscle paralysis---Sympathetic supply loss Leading to partial Ptosis and
    - With or without enophthalmos (inset eyeball)
- Horner syndrome is always IPSILATERAL.

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- Result from the lesion in the cervical spinal cord
- Occulomoter nerve palsy: Ptosis + Mydriasis while in Horner syndrome Ptosis + miosis.

## **Optic Nerve**

Optic nerve axon arises from the nerve cells of the Ganglionic layer of retina----it unites with the opposite nerve of the opposite side to form the Optic Chiasma----in optic Chiasma---fiber from medial (nasal) half of each retina cross the midline and enter the optic tract of the opposite side--whereas the fiber from the lateral (temporal) half of each retina pass posteriorly in the optic tract of the same side----most of the fiber of optic tract terminate by synapsing with nerve cell in lateral Geniculate body----few fibers pass to the pretectal nucleus and superior colliculus of the midbrain, however, and concerned with light reflex----the axon of the nerve cells of the lateral Geniculate body pass posteriorly as the optic radiation and terminate in the visual cortex of the cerebral hemisphere. The paraventricular pathway from the lateral Geniculate nucleus to the visual cortex is most sensitive for color contrast stimuli

# Naseem Sherzad High-Yield Points --- Lesion sites

- Lesion of the optic nerve causes blindness in the ipsilateral eye
- Lesion of the central (middle) part of the optic chiasm (often result of the pituitary tumor or meningioma) causes heteronymous Bitemporal hemianopia
- Bitemporal hemianopia is seen with aneurysm of the circle of Willis
- Lesion of the optic tract causes homonymous contralateral hemianopia
- Occlusion of the posterior cerebral artery results in homonymous hemianopia of the contralateral visual field with macular sparing
- Lesion of the geniculocalcarine tract causes homonymous hemianopia with macular sparing
- NOTE: How to solve the MCQs, which is given here: easy formula: Homonymous hemianopia in question--- will be converted into optic tract and the left of the question will be converted into right.

Nerve supply of Extraocular muscles: Mnemonic VSO4-HLR6 Rest 3

- -4th (Trochlear) cranial nerve, lesion cause Vertical Diplopia). -6<sup>th</sup> (Abducent) cranial nerve, lesion cause Horizontal Diplopia). Superior Oblique-----
- Lateral Rectus----
- Superior oblique———Having contralateral innervation, the trochlear nerve is unique among the cranial nerve in several aspects. It is the only cranial nerve that exits from the dorsal (rear) aspect of the brainstem. It innervates muscle the superior oblique muscle on the opposite side (contralateral) from its nucleus

# Oculomotor Nerve

- The Oculomotor nerve is the 3rd cranial nerve. It's a motor nerve only.
- General somatic efferent fibers: All extraocular muscles with the exception of lateral rectus (supplied by 6th cranial nerve) and superior oblique (supplied by 4th cranial nerve). The GSE fibers originate from the somatic component of the oculomotor nucleus (also termed the somatic motor
- General visceral efferent fibers: They originate from the parasympathetic component of oculomotor nucleus (also termed the Edinger Westphal nucleus). They supply the sphincter pupillae and ciliaris muscles. All these relay in the ciliary ganglion and are preganglionic parasympathetic fibers. The postganglionic parasympathetic fibers supply the sphincter pupillae and ciliaris muscles and originate from the ganglion.
- The oculomotor nerve originates from the anterior of the midbrain and appears in the interpeduncular fossa.
- The nerve then travel forwards, below the posterior cerebral artery and above the superior cerebellar artery, before piercing the dura mater and entering the cavernous sinus.
- Within the cavernous sinus, the oculomotor nerve is located uppermost, above the trochlear nerve in the lateral wall of the sinus.
- It enters the orbit via the superior orbital fissure as two branches: superior division and inferior division
- The superior division, the smaller of the two, runs above the optic nerve and gives branches to superior rectus and levator palpebrae superiaris muscles which it supplies with motor fibers. Additionally it also supplies the latter with sympathetic fibers derived from the internal carotid artery.
- The inferior division supplies the inferior rectus, medial rectus (this branch passes below the optic nerve), and the inferior oblique. It also gives off the parasympathetic root to the ciliary ganglion.
- Clinical consideration:
  - -Occulomoter nerve, by contraction of the ciliary muscle √ Accommodation—
  - ✓ Damage to Edinger Westphal nucleus result in loss of pupillary light reflex because Preganglionic fiber for constrictor papillae lies in Edinger westphal nucleus

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**Head And Neck** 

# Ptosis

- Ptosis with dilated pupil------Oculomotor nerve palsy
- Ptosis with constricted pupil------Horner syndrome
- · Amaurosis Fugax: it is caused by ischemia to the retina, often associated with carotid stenosis (ICA), and is a risk factor for stroke

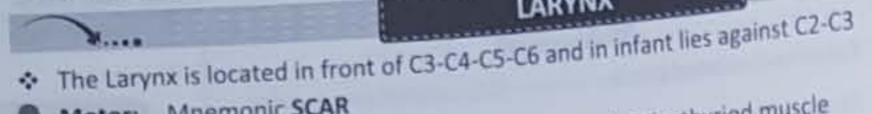
# **Pupillary Control**

Miosis (Excessive constriction of pupil)	Mydriasis (Dilation of pupil)	
Constriction, Parasympathetic	Dilation, sympathetic	
Ist neuron: Edinger-westphal nucleus     to ciliary ganglion via CN III	<ul> <li>Ist neuron: hypothalamus to the ciliospinal center of budge</li> </ul>	
2 <sup>nd</sup> neuron: short ciliary nerve to pupillary sphincter muscles	<ul> <li>2<sup>nd</sup> neuron: exit at T1 to superior cervical ganglion</li> <li>3<sup>rd</sup> neuron: plexus along internal carotid, through cavernous sinus, enter orbit along ciliary nerve to pupillary dilator muscles</li> </ul>	

# Important Eye Reflexes

Reflexes	Center	Afferent	Efferent
Accommodation reflexes	Cortex	Optic nerve	Oculomotor nerve
Pupillary light reflex	Mid-brain The olivary pretectal nucleus (OPN) is a midbrain structure that is part of the circuit mediating the pupillary light reflex	Optic nerve	Oculomotor nerve
Corneal reflex	Pons	Nasociliary branch of the ophthalmic division of the trigeminal nerve	Temporal and zygomatic branch of the facial nerve

# Chapter 5



# Motor: Mnemonic SCAR

- ✓ Superior laryngeal nerve (external branch)---only Cricothyriod muscle
- ✓ All other muscles is supplied by——Recurrent Laryngeal nerve
- ✓ LarynX is supplied by Xth (vagus) nerve

- ✓ Above the vocal cord: The internal laryngeal nerve— which passes between thyroid & hyoid Sensory:
- ✓ Below the vocal cord: The recurrent laryngeal nerve

# Superior laryngeal nerve a branch of vagus nerve divides into:

- ✓ Internal laryngeal nerve (sensory)
- ✓ External laryngeal nerve (motor & closely related to superior thyroid artery)

# Recurrent laryngeal nerve:

- ✓ It is a branch of the vagus nerve
- ✓ It is closely related to inferior thyroid artery.
- ✓ It Supplies all the muscles of the larynx, except Cricothyriod, the mucus membrane of the larynx below the vocal cord and the mucus membrane of the upper part of the trachea.
- ✓ The recurrent laryngeal nerves are the nerves of the sixth pharyngeal arch.
- ✓ Recurrent laryngeal nerve (RLN) injury results in true vocal-fold paresis or paralysis.

# Cricothyriod muscle:

- ✓ It is the tensor of the vocal cord.
- ✓ It is supplied by the external laryngeal nerve, Which is the most common nerve damage in thyroidectomy
- ✓ The Cricoid cartilage is derivative of the VIth Branchial arch.
- ✓ It is the only muscle outside the larynx

# Posterior Crico-Arytenoid:

- ✓ It is the only abductor of the vocal cord.
- ✓ Open the Glottis
- ✓ It is the safety muscle of the larynx
- ✓ Perhaps the most important muscle of the body

### Reflexes:

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- ✓ The afferent sensory nerve fibers for the cough reflex are contained in the vagus nerve.
- ✓ The afferent sensory nerve fibers for the Gag reflex are contained in the Glossopharyngeal. nerve.

# Histology:

- Type of epithelium lining the vocal cords is non-keratinizing stratified Squamous.
- Hyaline cartilage: thyroid, cricoid, Arytenoid expect the vocal process
- ✓ Elastic cartilage: the vocal process of Arytenoid, Corniculate, cuneiform, epiglottic cartilage.
- ✓ True vocal cords: stratified squamous epithelium with no/rare submucosal gland
- ✓ Epiglottis: stratified squamous epithelium

# Pathology:

- Phonation is produced by the vibration of vocal cords
- ✓ Bilateral abductor paralysis is an emergency where both vocal cards are present in the paramedian position and the patient has respiratory distress.
- ✓ The highest incidence of distant metastases in laryngeal cancer is seen in the Lung.
- Benign tumors are less common than the malignant tumor in the larynx.

# Laryngeal cartilage: 3 paired and 3 unpaired

# Cricoid cartilage: unpaired

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- ✓ Most inferior of laryngeal cartilage and completely encircles the airway, making the inferior. border of the larynx at the level of C6. It articulates with the paired Arytenoid cartilages posteriorly, as well as providing an attachment for the inferior horns of the thyroid cartilage.
- ✓ The cricoid is the only complete circle of cartilage in the larynx or trachea
- ✓ Inferior constrictor attached to it.

# Thyroid cartilage---- unpaired

- ✓ Largest of the laryngeal cartilage,
- ✓ The Adam's apple or laryngeal prominence is the lump or protrusion that is formed by the angle of the thyroid cartilage surrounding the larynx.
- · Epiglottis-----unpaired
- Arytenoid cartilages-----Paired
- . Corniculate-----Paired
- . Cuneiform-----Paired

**Head And Neck** 

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# **PHARYNX**



Head And Neck

- Sensory: Each of the three sections of the pharynx have a different innervations:
  - ✓ The nasopharynx is innervated by the maxillary nerve
  - ✓ The oropharynx by the Glossopharyngeal nerve
  - The laryngopharynx by the internal laryngeal nerve, branch of the superior laryngeal branch of the vagus nerve
- Motor:

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All the muscles of the pharynX are innervated by the vagus nerve (CN X), except for the stylopharyngeus, which is innervated by the Glossopharyngeal nerve (CN IX).

# **Tonsil Histology**

- Palatine-----Stratified Squamous epithelium, located in isthmus of the fauces between palatoglossus and palatopharyngeus, the two arches of the soft palate
- -Pseudo-stratified ciliated columnar epithelium Pharyngeal-
- -stratified squamous epithelium Lingual-

## Salivary Gland

- . Three nerves lie close to the submandibular gland that can be damaged during their removal, the marginal mandibular branch of the facial nerve, lingual nerve and hypoglossal nerve. The marginal mandibular branch of the facial nerve is the most likely to be damaged during submandibular gland removal.
- . The percentage of salivary calculi seen in the submandibular gland is 80%.
- . Major amount of saliva, when salivary gland are not stimulated are contributed by submandibular gland.
- . The Most common site of origin of pleomorphic adenoma is the Parotid gland.
- Tumor of the hard palate usually arise from the minor salivary gland
- . The Most common malignant tumor of the submandibular salivary gland is adenoid cystic carcinoma, which has a tendency for perineural invasion.
- . The Common cause of the salivary gland atrophy is the obstruction of the excretory duct
- Salivary gland have dual autonomic supply but not reciprocal supply
- Small minor/unnamed salivary gland located in the submucosal layer with short duct opening directly onto the mucosal surface

# Submandibular gland

- Divided by Mylohyoid muscle into superficial and deep parts
- The submandibular duct emerges from the medial side of the deep part of the gland in the oral cavity and passes forward to open on the summit of a small sublingual papilla beside the base of frenulum of the tongue
- The submandibular duct or Wharton duct is the most common site for sialolithiasis

Parotid gland

- Largest among salivary gland, secretion is very rich of amylase
- The Posteromedial surface of the parotid gland is closely related to carotid fascia
- Secretary epithelium of parotid gland is derived from endoderm
- PAST----PA-Parotid, Pure serous---ST----STensen duct
- The parotid duct passes anteriorly across the external surface of the Masseter muscle and then turns medially to penetrate the Buccinator muscle of the cheek and open into the oral cavity adjacent to the crown of the second upper molar tooth.
- Obstruction of the duct will cause shrinking of parotid gland because of the process of apoptosis
- Structure from lateral to medial----FRE
  - √ Facial nerve---most superficial
  - ✓ Retromandibular vein
  - ✓ ECA---most medial
- Clinical notes:

- ✓ Frey's Syndrome is a syndrome that includes sweating and facial flushing while eating (gustatory sweating).
- ✓ It is caused by injury to a nerve, called the Auriculotemporal nerve, typically after surgical trauma (superficial parotidectomy).

#### Histology

- Mixed salivary gland: Contain both serous and mucous secretory unit. Sometime serous cells form Crescentric caps on mucous acini called as serous demilunes.
  - ✓ Submandibular gland (Mixed: 90% serous, 10% Mucous), serous primarily
  - ✓ Sublingual gland (predominant mucous acini; some serous demilunes), mucous primarily
- · Parotid gland: Serous acini only

# Tongue



# Embryology

- Extrinsic plus intrinsic muscle -----From occipital somite
- Tongue Tie is best corrected at-----3-4 years

# **Blood supply**

Lingual----This is the major artery of the tongue

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- Tonsiller artery
- Ascending pharyngeal artery

NAME AND ADDRESS OF THE OWNER, WHEN PERSON NAMED IN

### Muscle

NAME AND ADDRESS OF THE OWNER, WHEN PERSON NAMED IN \* Except for the palatoglossus, which is innervated by the vagus nerve, all muscles of the tongue are innervated by the hypoglossal nerve

# Muscles:

- > Intrinsic muscle
  - ✓ The intrinsic muscles of the tongue originate and insert within the substance of the tongue. They are divided into superior longitudinal, inferior longitudinal, transverse, and vertical muscles,

**Head And Neck** 

# Chapter 5

## > Extrinsic muscle:

- ✓ There are four major extrinsic muscles on each side, the Genioglossus, Hyoglossus, Styloglossus, and palatoglossus. These muscles protrude, retract, depress, and elevate the ✓ The Styloglossus muscles retract the tongue and pull the back of the tongue superiorly
- The Hyoglossus muscle is an important landmark in the floor of the oral cavity
- √ Genioglossus:
- O Protrude the anterior part of the tongue out of the oral fissure (i.e. 'stick the tongue out'). And depress the central part of the tongue

# Nerve supply

#### Anterior two-third

- ✓ General sensation-----Lingual nerve
- ✓ Taste sensation (special visceral afferent- SVA)---Chorda tympani nerve --7<sup>th</sup> nerve branch

#### · Posterior one third

✓ Both general & taste sensation are carried by: Glossopharyngeal nerve

## Lymph drainage

- Submental lymph node———Tip of tongue
- Submandibular lymph node———Anterior 2/3<sup>rd</sup> and side of tongue
- Deep cervical lymph node------Posterior 1/3rd
- All lymphatic vessels from the tongue ultimately drain into the deep cervical chain of nodes along the internal jugular vein

# **Primary Gustatory Cortex**

- The Lower end of postcentral gyrus in the superior wall of the lateral sulcus
- Brodmann area 43

NAME AND POST OFFICE ADDRESS OF TAXABLE PARTY.

NAME AND ADDRESS OF TAXABLE PARTY.

# Taste pathway

#### First order neuron:

- ✓ From anterior 2/3 of tongue---lingual nerve----Chorda tympani-----facial nerve----tractus solitarious (contain 2<sup>nd</sup> neuron)
- ✓ From posterior 1/3 of tongue-----Glossopharyngeal nerve----tractus solitarious
- ✓ From the base of tongue and pharynx-----vagus nerve-----tractus solitarious

## 2<sup>nd</sup> order neuron:

✓ From nuclei of tractus solitarious to the VPM of the thalamus

# # 3<sup>rd</sup> order neuron:

NAME AND POST OFFICE ADDRESS OF THE OWNER.

From thalamus to the primary gustatory area (43) located at the base of the postcentral gyrus superior to the lateral cerebral sulcus in the parietal cortex

# Papillae and Primary sense of tastes

The papillae in general increase the area of contact between the surface of the tongue and the contents of the oral cavity. All except the Filiform papillae have taste buds on their surfaces.

# Filiform papillae:

Chapter 5

- Small cone-shaped projections of the mucosa that end in one or more points
- Smallest and the most numerous
- No taste buds, absent in erythema margins
- Present on the dorsal surface of the tongue

# Fungiform papillae:

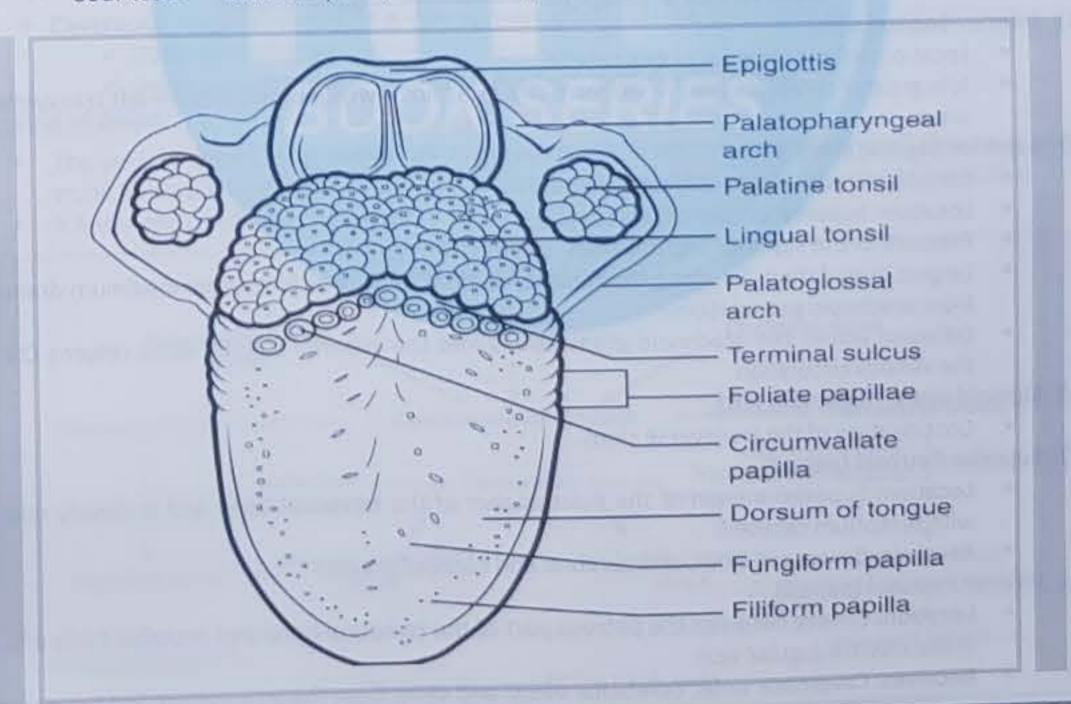
- Concentrated along the margins of the tongue and tip of the tongue
- Salty taste detected by------Anterior half of each side of tongue
- Sweet taste caused by (sugar, Glucose, Alcohols, aldehydes, ketoneetc-----detected by-------- Tip of tongue
- Umami

# Cicumvallate papillae:

- The largest of the papillae are the vallate papillae, which are blunt-ended cylindrical papillae in invaginations in the tongue's surface-there are only about 8 to 12 vallate papillae in a single V-shaped line immediately anterior to the terminal sulcus of tongue
- Bitter taste causes by------ Alkaloid, Quinine, Caffeine and nicotine----- mediated by Gprotein-----detected by the back of the tongue
- Supplied by Glossopharyngeal nerve (CN 9<sup>th</sup>)

# Foliate papillae:

- Are linear folds of mucosa on the sides of the tongue near the terminal sulcus of tongue
- Sour taste----caused by acid, detected by posterior half of tongue



**Head And Neck** 

## Lymphatic System of Head and Neck

### Parotid node:

Situated on or within the parotid salivary gland

They receive lymph from: Scalp above the parotid gland, the eyelids, the auricle and the external auditory meatus

### Submandibular lymph node:

- Lies superficial to the submandibular salivary gland just below to the body of the mandible
- They receive lymph from: Front of the scalp, the nose, the cheek, the upper and lower teeth (except the lower incisor) the frontal, the maxillary, and the Ethmoid sinus, the anterior 2/3rd of tongue (except tip) the floor of the mouth, and the vestibule and the gums

### Submental lymph node

- Lies in the submental triangle just below the chin
- They receive lymph from: the tip of the tongue, the floor of the anterior part of mouth, the central part of the lower lip and the skin over the chin

### Deep cervical lymph nodes:

- Arranged in a vertical chain along the course of the internal jugular vein within the carotid sheath
- The efferent lymph vessels from all the deep cervical lymph nodes join to form the jugular trunk, which drains into the thoracic duct or right lymphatic duct.
  - o Jugulo-digastric node: lies behind the angle of the jaw and drains the tonsil
  - Jugulo-Omohyoid: it is mainly associated with drainage of the tongue

#### **Dural Venous Sinuses**

---dural sinuses Brain venous drainage to----

### 1) Inferior Sagittal sinus

- · Location: Inferior margin of falx cerebri
- Join greater cerebral vein——to form straight sinus—which drains into——left transverse sinus

### 2) Superior Sagittal sinus

- Continuous with right transverse sinus
- Location: Superior border of falx cerebri
- Pressure in the superior sagittal sinus is minus 10
- Largest granulations lie along the superior sagittal sinus, which receives maximum drainage from arachnoid granulation
- Diffusion across the arachnoid granulations into the superior sagittal sinus returns CSF to the venous circulation

### 3) Sigmoid sinus: (Right and left)

Continuation of the transverse sinus

### 4) Superior Petrosal (paired)

- Location: Superior margin of the petrous part of the temporal bone and is closely related with tentorium cerebelli
- Receives: Cavernous sinus, and cerebral and cerebellar veins

### 5) Inferior Petrosal (paired)

- Location: Groove between the petrous part of the temporal bone and occipital bone ending in the internal jugular vein
- Receives: Cavernous sinus, cerebellar veins, and veins from the internal ear and brainstem

### Chapter 5

**Head And Neck** 

### 6) Cavernous sinus: (Paired)

- Location: lateral aspect of the sphenoid bone in the middle cranial fossa
- Numerous trabeculae cross their inferior, give them a spongy appearance
- Connecting the right and left cavernous sinuses are the intercavernous sinuses on the anterior and posterior sides of the pituitary stalk
- The cavernous sinuses receive blood not only from cerebral veins, but also from the ophthalmic veins (from the orbit) and emissary veins (from the pterygoid plexus of veins in the infratemporal fossa) and superficial middle cerebral vein also end in the cavernous sinus

### Two important differences:

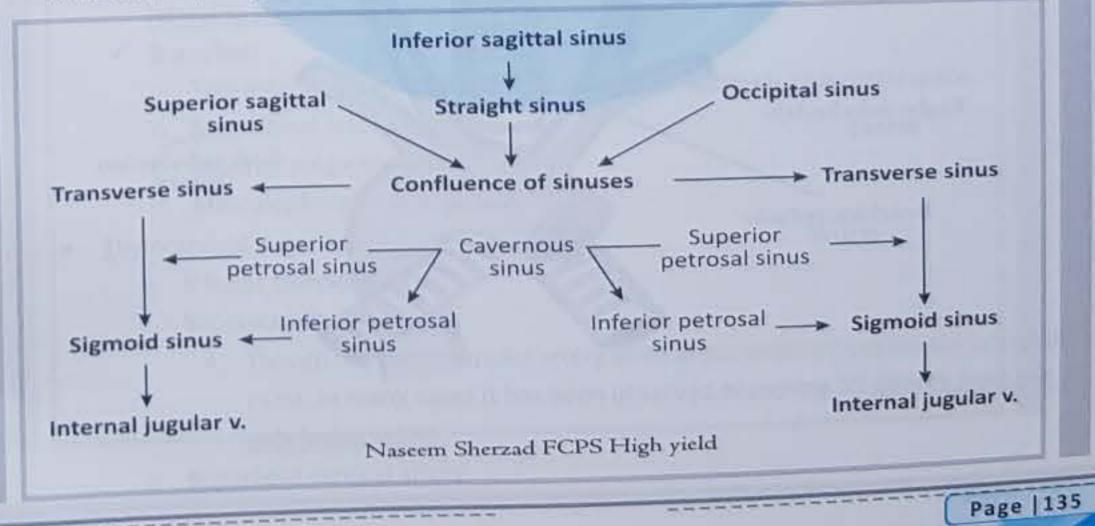
- ✓ Cavernous sinus infection by-----Inferior Ophthalmic Vein
- ✓ Cavernous sinus thrombosis by-----Superior Ophthalmic Vein

### Contents: -----O TOM CAT----- Mnemonic :

- ✓ TOM are lateral wall components, in order from superior to inferior.
- ✓ CA are the components within the sinus, from medial to lateral. CA ends at the level of T from O TOM.
  - O O-----Occulomoter nerve
  - T-----Trochlear nerve
  - O O-----Ophthalmic nerve
  - o M-----Maxillary nerve
  - C-----Carotid artery (internal)
  - O A-----Abducent nerve
  - o T: When written, connects to the T of OTOM.
- Cavernous sinus syndrome:(e.g. due to mass effect, fistula, thrombosis)
  - ✓ Ophthalmoplegia
  - ✓ Decrease corneal and maxillary sensation with normal vision

### 7) Vein of Galen:

- The vein of Galen, also known as the great cerebral vein or great vein of Galen, is a short trunk formed by the union of the two internal cerebral veins and basal veins of Rosenthal.
- It lies in the quadrigeminal cistern.

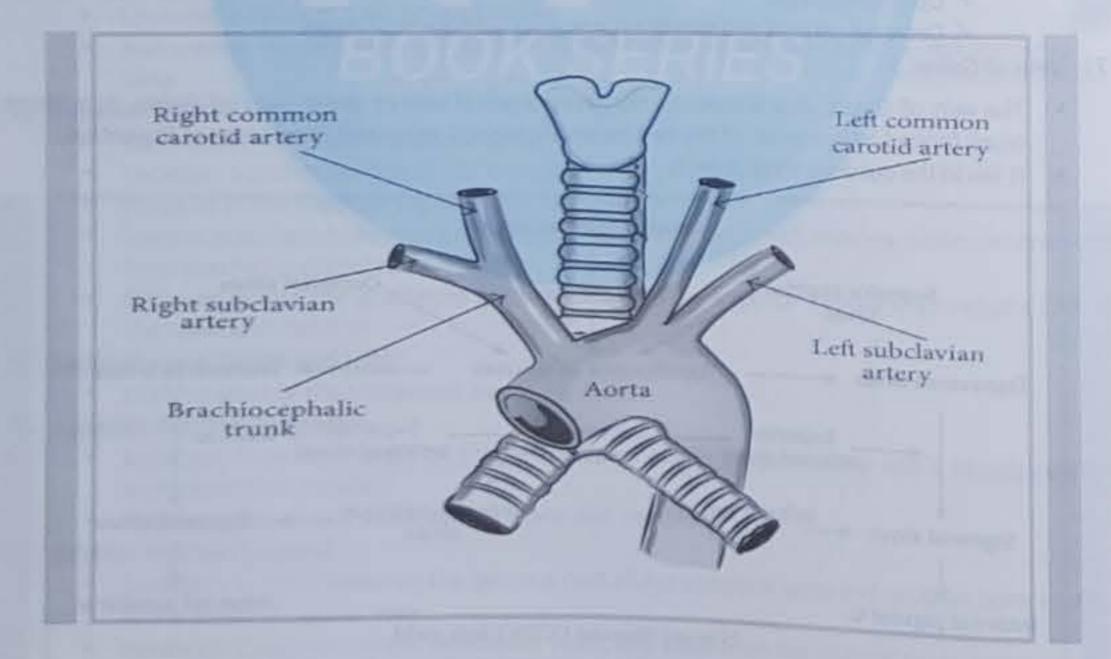


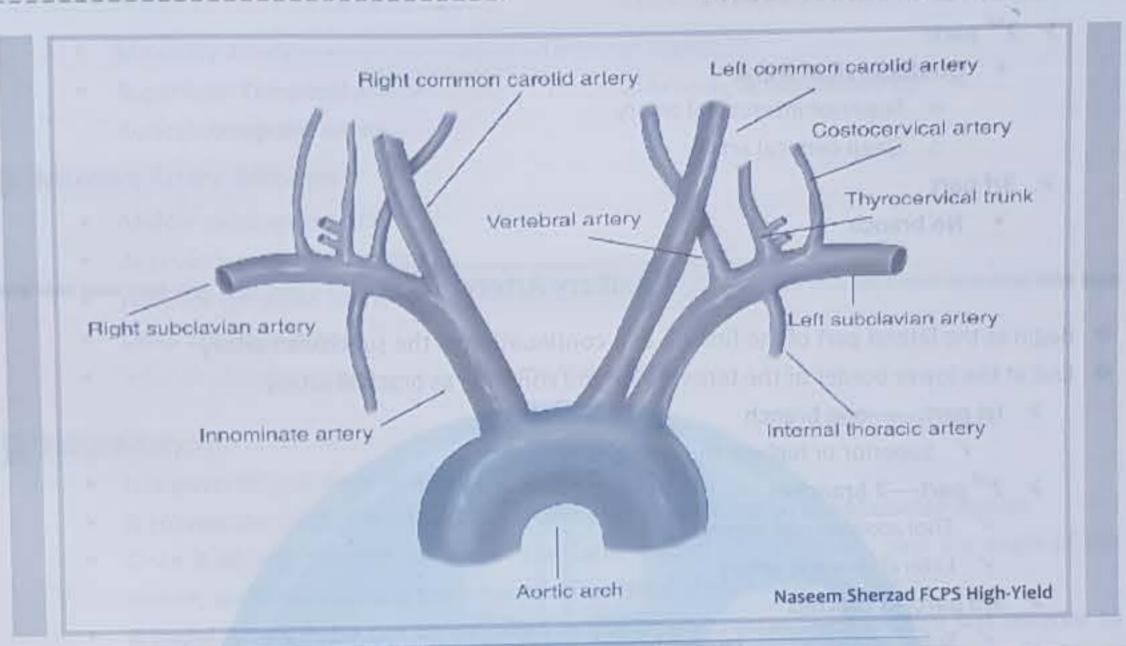
### **Arterial System**



### ABC'S of the Aortic Arch

- Aortic arch gives off the Brachiocephalic trunk, then the left Common Carotid, and then the left Subclavian artery
- \* Right side: Brachiocephalic artery (or brachiocephalic trunk or innominate artery):
  - The brachiocephalic artery arises from the aortic arch at the level of the second right costal cartilage. Then it runs upwards to the right and at the border of the right sternoclavicular joint divides into:
    - ✓ Right Subclavian artery
    - ✓ Right Common Carotid artery
- . Left side: Direct from the arch of aorta
  - Left common carotid artery——just a little away from the midline
  - Left subclavian artery
- The commonest variation in the arteries arising from the arch of the aorta is that left common carotid artery arising from the brachiocephalic trunk





### Subclavian Artery

- Scalenus anterior is used to divide subclavian artery into three parts that's why Scalenus anterior is more important as a landmark than an active muscle
- Subclavian artery Make groove on the first rib that's why it is affected in first rib fracture

### Branches: VIT-C

- > Ist part:
- Vertebral artery

- Internal thoracic artery
  - ✓ It ascends <u>vertically on the pleura behind the coastal cartilage. One fingerbreadth</u>

    lateral to sternum and end at intercostal space
  - ✓ Branches:
    - Two anterior intercostal arteries: it supplies upper six intercostal space
    - Mediastinal arteries
    - Superior epigastric artery
    - Musculopherenic artery
- Thyrocervical trunk: ISS
  - Inferior thyroid artery
  - o Suprascapular artery:
    - Though the suprascapular artery often arises directly from the thyrocervical trunk, in many cases it has been observed branching off <u>directly from the</u> subclavian artery.
  - Superficial cervical artery

### **Head And Neck**

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- > 2<sup>nd</sup> part:
  - Costocervical trunk
    - Superior intercostal artery
    - Deep cervical artery
- > 3rf part
  - No branch

### **Axillary Artery**

- NAME AND POST OFFICE ADDRESS OF THE OWNER. \* Begin at the lateral part of the first rib as a continuation of the subclavian artery
- End at the lower border of the teres major and continue as brachial artery
  - > Ist part:----one branch
    - ✓ Superior or highest thoracic artery
  - > 2<sup>nd</sup> part---2 branches
    - √ Thoracoacromial artery
    - ✓ Lateral thoracic artery
  - > 3rd part---3 braches
    - ✓ Subscapular-artery-largest branch, involved in shoulder joint anastomoses
    - ✓ Anterior circumflex Humeral artery
    - ✓ Posterior circumflex Humeral artery

### Internal Carotid Artery

- At origin, internal carotid artery is lateral to external carotid artery then go posteriorly and become medial in the rest of the course. Immediately enter to cavernous sinus
- . Lateral to optic Chiasma terminate into the anterior and middle cerebral artery
- Give No branches in the neck

WHEN PERSON NAMED IN COLUMN 1 IS NOT THE OWNER.

### External Carotid Artery (ECA)

- . Begin at the level of the upper border of the thyroid cartilage
- . Terminate in the substance of parotid gland into the superficial temporal artery and maxillary artery behind the neck of the mandible
- Give all branches in the neck
- \* External carotid artery branches: "Some Angry Lady Figured Out PMS"----8
  - Superior thyroid artery————Anterior
  - Ascending Pharyngeal artery------Medial
  - Lingual artery------Anterior: it runs obliquely deep to the posterior digastric and near palatoglossus muscle
  - Facial artery
  - Occipital artery------Posterior
  - Posterior auricular artery-----

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### Chapter 5

**Head And Neck** 

- Maxillary artery------Terminal branch
- Superficial Temporal artery-----Terminal branch, accompanied by Auriculotemporal nerve

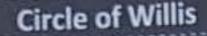
### Maxillary Artery: branches

- Middle meningeal artery
- Accessory meningeal artery
- Anterior tympanic branch
- Deep auricular branch
- Inferior alveolar artery------Give mental artery

#### Facial Artery:

- It is given off just deep to the angle of the mandible.
- It crosses the inferior border of the mandible just anterior to the Masseter muscle
- Once it on the anterior surface of the face, it goes up the cheek, past the angle of the mouth, and heads toward the inner canthus (medial corner) of the eye.
- A Facial Artery Pulse can be palpated as the artery crosses the mandible just anterior to the Masseter muscle.
- Branches of the Facial Artery:
  - ✓ Superior Labial Branch above mouth----Has anastomoses with the Infraorbital Artery
  - ✓ Inferior Labial Branch below the mouth
  - ✓ Angular Artery heads up to the nose-----Has anastomoses with the Ophthalmic Artery
  - ✓ Lateral Nasal Branch
- . Carotid endarterectomy: Loss of cervical nerve sensation is always present after carotid endarterectomy but tends to improve with time. However, the timing and extent of this improvement is unpredictable. When disregarding the frequently injured cutaneous cervical nerve, the nerves at potential risk include facial, Glossopharyngeal, vagus, accessory, and hypoglossal nerve. The hypoglossal nerve appears to be the most susceptible to injury because of its proximity to the carotid bifurcation followed by vagal nerve injury
- . After Denervation of the carotid chemoreceptors, the response to a drop in PO2 is abolished, the predominant effect of hypoxia after Denervation of the carotid bodies is a direct depression of the respiratory center. The response to change in arterial blood H<sup>+</sup> concentration in the pH 7.3-7.5 range is also abolished, although larger changes exert some effect. The response to change in arterial PCO2, on the other hand is affected slightly; it is reduced no more than 30-35%. So Denervation of the carotid body has the least effect on PCO2
- . Compression of the facial artery on one side doesn't stop bleeding from a lacerated facial artery or one of its branches that's why In laceration of the lip, pressure must be applied on both sides of the cut to stop bleeding from facial artery bilaterally

THE RESERVE NAMED IN COLUMN 2 ISSUED TO THE OWNER.



### Vertebral Artery: Contribute 20%

- The vertebral arteries arise from the subclavian arteries, one on each side of the body
- Then enter deep to the transverse process at the level of the 6th cervical vertebrae
- · Branches:
- Anterior spinal artery: (ASA)
  - It arises from branches of the vertebral arteries and courses along the anterior aspect of the spinal cord.
  - Occlusion of ASA lead to Medial Medullary syndrome
  - Medial Medullary syndrome present with a lesion of the hypoglossal nerve (deviation of the tongue on protrusion toward the side of the lesion) and lesions to both the medial lemniscus and the corticospinal tract

### PICA

- The Posterior inferior cerebellar artery (PICA), the largest branch of the vertebral artery,
   supply dorsolateral surface of the medulla
- PICA give posterior spinal artery (PSA)
- Occlusion of PICA lead to lateral Medullary syndrome
- Lateral Medullary (Wallenberg) syndrome: The cranial nerve of nuclei involved in this
  lesion is the vestibulo or cochlear part of CN 8 (May produce nystagmus, vertigo, nausea
  and vomiting), Glossopharyngeal nerve (result in diminished or absent gag reflex) and the
  vagus nerve (may produce dysphagia, or hoarseness), and the spinal nucleus tract of CN 5.
  The long tracts involved are the Spinothalamic tract and the descending hypothalamus
  fibers.

### Basilar artery:

- The two vertebral arteries join to form the basilar artery
- Occlusion lead to Medial Pontine syndrome
- Medial pontine syndrome: At a minimum, this lesion affects the exiting fibers of the Abducent nerve (result in <u>Diplopia</u> on attempted lateral gaze to the affected side) and the corticospinal tract and corticobulbar tracts (symptoms like quadriplegia, loss of voluntary facial, mouth and tongue movements)
- · AICA:
  - ✓ Branch of the basilar artery
  - ✓ Labyrinthine artery: The labyrinthine artery a long slender branch of the AICA (85%-100% cases) or basilar artery (<15% cases)
    </p>
  - ✓ Occlusion leads to the lateral pontine syndrome
  - Lateral pontine syndrome: The cranial nerve involved will be the facial (produce ipsilateral facial paralysis, loss of taste from anterior 2/3<sup>rd</sup> of the tongue, loss of lacrimation and salivation, and loss of corneal reflex) and vestibulocochlear in the caudal pons, the trigeminal nerve in the rostral pons and the spinal nucleus and tract of V in both lesion

Chapter 5 Head And Neck

#### Posterior cerebral arteries

- ✓ The basilar artery terminates by splitting into the left and right posterior cerebral arteries
- ✓ The posterior cerebral artery supplies the occipital lobe(visual area), the inferior part
  of the temporal lobe, and various deep structure including the thalamus

### Internal Carotid Artery: Contribute 80%

Entering the cranial cavity, each internal carotid artery gives off the:

### Ophthalmic artery

### Posterior communicating artery:

- Basilar artery and ICA communicate with each other by posterior communicating artery
- The posterior communicating artery run back from the <u>internal carotid artery above the</u>
   oculomotor nerve, and anastomoses with the posterior cerebral artery (a terminal branch
   of the <u>basilar artery</u>)

### Middle cerebral artery:

- The middle cerebral artery is the largest branch of the internal carotid
- It supplies:
  - The bulk of the lateral surface of the hemisphere; except for the superior inch of the frontal and parietal lobe (anterior cerebral artery), and the inferior part of the temporal lobe.
  - Anterior temporal lobes and the insular cortices.
  - ✓ The artery supplies a portion of the frontal lobe and the lateral surface of the temporal and parietal lobes, including the primary motor and sensory areas of the face, throat, hand and arm, and in the dominant hemisphere, the areas for speech.
  - √ Broca's area
  - ✓ Wernicke's area---- Superior temporal gyrus
  - ✓ Deep branches supply the basal ganglia as well as the internal capsule
  - ✓ Arterial supply of motor area of the cerebral cortex is by both anterior and middle cerebral artery
  - ✓ MCA occlusion site and resulting Aphasia
    - o Global -the trunk of MCA
    - Broca the anterior branch of MCA
    - Wernicke the posterior branch of MCA

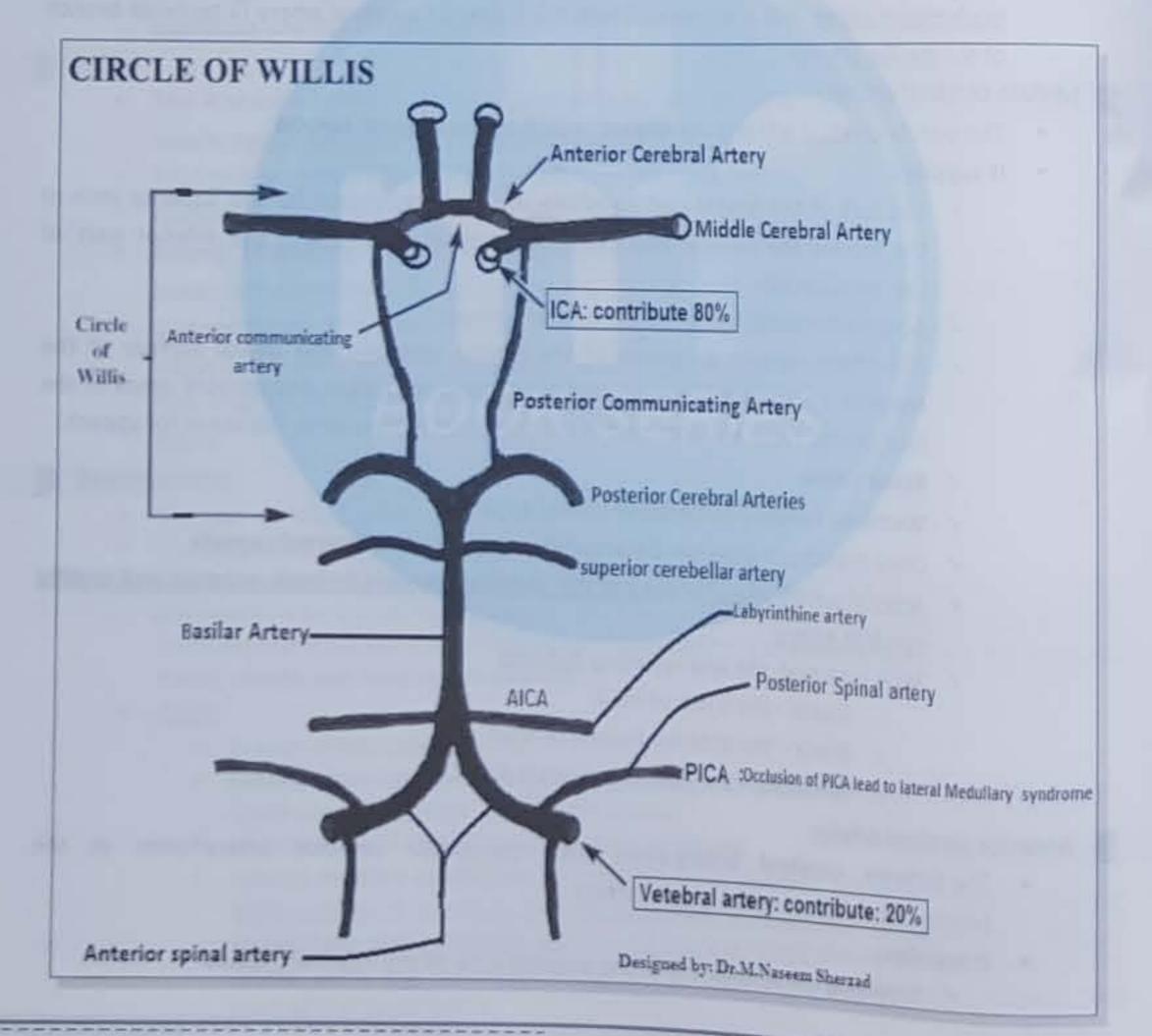
### Anterior cerebral artery:

- The anterior cerebral artery along with the middle cerebral artery forms at the termination of the internal carotid artery.
- . It supplies:
  - ✓ Supplying the ventral half of the anterior limb of the internal capsule

- ✓ Supplying the pre-frontal area. This is the area of mentality and inhibition of primitive reflexes
- ✓ Supplying the motor and sensory areas of the Lower limb, and the paracentral lobule (cortical bladder center).
- Supplying the corpus callosum.
- ✓ Cingulate gyrus

### Anterior choroidal artery:

The Anterior choroidal artery is the most distal branch of the ICA, originates just after the origin of the posterior communicating artery, and courses posterolaterally to supply the anterior medial temporal lobe, the optic tract, the Geniculate body, the medial globus pallidus, The medial third of the cerebral peduncle, portions of the ventral and pulvinar thalamus and the posterior limb of the internal capsule



Chapter 5

**Head And Neck** 

### Venous system

### Internal Jugular vein (IJV)

- It starts as a continuation of the sigmoid venous sinus and leaves the skull through the jugular foramen. The internal jugular vein is the biggest vein of the neck. The right internal jugular vein is generally bigger compared to the left
- Throughout its course, it is closely related with deep cervical lymph nodes.
- It starts from ear lobules to Sternoclavicular joint.
- Unite with subclavian vein behind the middle of the clavicle and form the brachiocephalic vein
- IJV after leaving Jugular foramen has immediate relation with ICA
- Tributaries: IPL-MSF
  - ✓ Inferior Petrosal vein
  - √ Pharyngeal vein
  - ✓ Lingual vein
  - ✓ Middle thyroid vein
  - √ Superior thyroid vein
  - √ Facial vein

### External Jugular Vein (EJV)

- It begins on the surface of Sternocleidomastoid muscle behind the angle of the jaw, in the substance of the parotid gland, by the union of the posterior auricular vein and posterior division of Retromandibular vein
- After its formation, it runs downwards over the sternocleidomastoid, and reaches the posterior border of the muscle about an inch above the clavicle.
- There, It pierces the deep fascia, and descends close to the Sternocleidomastoid muscle, to end in the subclavian vein behind the middle clavicle.
- It has valves
- **Tributaries: PAST** 
  - ✓ Posterior external jugular vein
  - ✓ Anterior jugular vein—a terminal tributary of EJV, which join subclavian vein
  - ✓ Suprascapular vein
  - √ Transverse cervical vein

### Subclavian vein:

- It is the continuation of Axillary vein at the outer border of the first rib.
- It joins the internal jugular vein to form brachiocephalic vein and it receives the EJV.
- In addition, it often receives the thoracic duct on the left side and the right lymphatic duct on

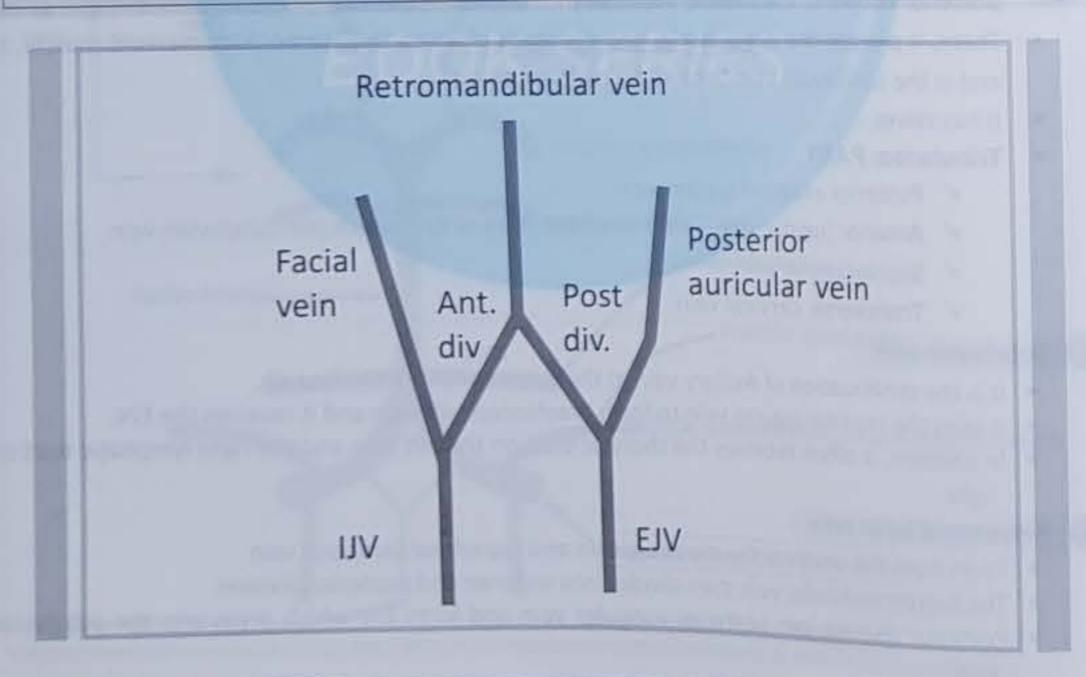
### Retromandibular vein:

- Form from the union of the maxillary vein and superficial temporal vein
- The Retromandibular vein then divides into anterior and posterior division
- Posterior division join posterior auricular vein and form EJV which drain into the subclavian vein

- Anterior division join facial vein and drain into the IJV
- Facial vein form at the medial angle of the eye from the union of supraorbital and supratrochlear veins

## Naseem Sherzad High-Yield Points

- Infection from middle ear spread to IJV
- Surgical removal of the deep cervical node can puncture IJV
- For Central venous line or catheter most often use Right IJV
- The RIJV is preferred over the left-sided internal jugular vein (LIJV) because cannulation of the LIJV is more difficult and associated with a higher complication rate
- . Compression of both jugular vein cause intracranial pressure to rise then fall
- \* Facial vein is formed from the Supraorbital + Supratrochlear Veins
- \* Superior Ophthalmic Vein is a communication between the Facial Vein and the Cavernous Sinus
- . Deep Facial Vein is a communication between the Facial Vein and the Pterygoid Plexus.
- The Facial Vein has no valves. Backflow can cause infection to get into the dural sinuses, through the Deep Facial Vein (via pterygoid plexus) And Superior Ophthalmic Vein (via Cavernous Sinus)
- . Danger triangle of the face: A triangle approximately covering the nose and maxilla, and going up to the region between the eyes. Superficial Veins communicate with dural sinuses in this region.



Chapter 5

**Head And Neck** 

### Embryology of Head And Neck



Region of the face that are derived from the various embryological structures

Processes	Structure Formed	
<ul> <li>Frontonasal process</li> </ul>	Forehead, bridge of nose, medial and lateral nasal prominence	
<ul> <li>Maxillary process</li> </ul>	❖ Cheeks, the lateral portion of upper lip	
❖ Medial nasal process	Philtrum of upper lip crest and the tip of the nose	
<ul> <li>Lateral nasal process</li> </ul>	❖ Ala of the nose and lateral nasal wall	
<ul> <li>Mandibular process</li> </ul>	❖ lower lip and jaw	

### Cleft lip:

- It is a multifactorial genetic disorder that involves neural crest cell
- The most common congenital anomaly of the head is cleft lip and cleft palate
- Cleft lip result from the following:
  - ✓ Median/midline cleft lip: It results from failure of fusion of two medial nasal prominences to form
  - ✓ Unilateral cleft lip: The maxillary prominence fail to fuse with Medial nasal prominence
  - ✓ The underlying mesoderm and neural crest fail to expand, resulting in the persistent labial groove
- If the medial part of upper lip incompletely formed (median cleft) than orbicularis oris muscle will insert on ala of the nose
- The typical distribution of cleft types is: (Reference: Bailey & love 27th edition P.688)
  - ✓ Cleft lip alone: 15%
  - Cleft lip and palate: 45%
  - ✓ Isolated cleft palate: 40%

### Cleft palate:

- It is a multifactorial genetic disorder that involves neural crest cell
- Cleft palate is classified into anterior and posterior
- The anatomic landmark that distinguishes an anterior cleft palate from the posterior cleft palate is the incisive foramen
- Anterior cleft palate: occur when palatine shelves fail to fuse with the primary palate
- Posterior cleft palate; occur when the palatine shelves fail to fuse with each other and with the nasal septum
- Feeding difficulty occurs more with cleft palate abnormalities. The infant may be unable to suck properly because the roof of the mouth is not formed completely.

## Clinical Notes, Landmarks and Mnemonics



### MALES

- M——Medial Geniculate body, a thalamic nucleus which relays auditory impulses, is separated from the main mass of the thalamus and lies on the midbrain pathway
- A ———Auditory: ———Inferior colliculus and sublenticular fiber
- . L----Lateral Geniculate body
- . E----EYE
- Superior colliculus and retrolenticular fiber

### Superior Colliculus:

- It is involved in the generation of rapid eye movements called saccades that are used several times per second to shift the gaze to different parts of the visual field.
- It is responsible for the reflex movements of the eye, head and neck in response to visual stimuli
- Lesion of superior colliculus: Lesion of the LEFT superior colliculus results in inability to turn head reflexively to the RIGHT (CONTRA.) upon visual (or somatosensory and auditory) stimuli on the RIGHT.

### MALE---Content of foramen OVALE

- M------Mandibular nerve
- A ————Accessory meningeal artery
- L-----Lesser Petrosal nerve
- E-----Emissary vein (connecting extracranial vein with intracranial vein)
- Otic ganglion lies under foramen oval

### The Angle of the mandible:

- Supplied by the greater auricular nerve(also supply Pinna of the ear)
- The facial artery can be palpated here
- EJV form near the angle of the mandible when Retromandibular and posterior auricular vein join
- The most common presentation of parotid gland tumor is that it present as a Mass behind the angle of the mandible

### The Neck of the mandible

- Parotid gland lies here
- External carotid artery divided here

### st rib outer border

Subclavian artery become Axillary artery here

### Superior olivary nuclei:

- Group of nuclei located in the brainstem near the junction of the pons and medulla. It is
  the first auditory relay after the cochlear nucleus on the way to the auditory cortex and is
  the major point at which information from the two ears is integrated.
- Used to locate sound, detecting the direction from which the sound is coming

### Chapter 5

### **Head And Neck**

### Ganglions

### 1) Pterygopalatine ganglion:

- The Pterygopalatine ganglion is also known as Sphenopalatine ganglion, largest parasympathetic ganglion which is suspended from the maxillary nerve in the pterygopalatine fossa
- Greater Petrosal nerve--------Pterygopalatine ganglion—secretomotor fiber to <u>lacrimal</u>
  gland and gland of the nose
- Clinical notes: Damage to pterygopalatine ganglion cause Dry eye due to decreased tear production from the lacrimal gland

### 2) Submandibular ganglion:

- Small, fusiform in shape and parasympathetic ganglion
- Chorda tympani combine with the lingual nerve in temporal fossa----submandibular ganglion

### 3) Otic ganglion: Glossopharyngeal nerve

- Lies under foramen Ovale
- Tympanic nerve------form tympanic plexus-----give lesser Petrosal nerve--------
  Give GVE pre-ganglionic parasympathetic fiber to-------otic ganglion-----
  Auriculotemporal nerve to--------parotid gland
- The tympanic nerve communicates with the cranial nerve IX and passes as the lesser petrosal nerve through the petrotympanic fissure.

### 4) Trigeminal ganglion:

- The Trigeminal ganglion is located in the middle cranial fossa.
- It is situated in a fold of dura mater that forms an invagination around the posterior twothirds of the ganglion. This region is referred to as the Meckel cavity and contains cerebrospinal fluid.
- The ganglion is bound medially by the cavernous sinus and optic and trochlear nerves; superiorly by the inferior surface of the temporal lobe of the brain; and posteriorly by the brain stem. Access to the ganglion requires passage of the block needle through foramen ovale.
- Clinical notes: After recovery from a primary herpes infection, the virus is not cleared from the body, but rather lies dormant in a non-replicating state within the trigeminal ganglion

### 5) Ganglion associated with facial nerve:

- Pterygopalatine ganglion (parasympathetic ganglion)
- Submandibular ganglion (parasympathetic ganglion)
- Geniculate ganglion (sensory ganglion), located in the facial canal

### Head And Neck

Chapter 5

- Origin from medulla oblongata-----9,10,11,12
- Sensory Cranial Nerves------1,2,8
- Cranial nerve which contains only afferent (Sensory fiber) fibers----1,2,8
- The Cranial nerve which contains only efferent (motor) fibers------3,4,6,11, 12
- Only two nerve decussate——2 and 4
- The Cranial nerve in the floor of 4<sup>th</sup> ventricle————6,8,12
- Parasympathetic cranial nerve-----3-7-9-10
- Vitamin K-dependent clotting factors----2-7-9-10
- Smallest Cranial Nerve, Cranial Nerve with Longest Intra-Cranial Course and Cranial Nerve
   Emerging From Dorsal Aspect of Brainstem————Trochlear
- Largest Cranial Nerve and Thickest Cranial Nerve ————Trigeminal
- Cranial Nerve with Direct Projection to Cerebral Cortex-----Olfactory
- Cranial Nerve with Longest Intra-Osseous Course———Facial Nerve
- Cranial Nerve Effected in Pyogenic Meningitis------CN VIII
- Cranial Nerve Effected in Multiple Sclerosis———Optic Nerve.
- The nerve of the pterygoid canal (Vidian nerve) is formed by the junction of the greater petrosal nerve and the deep petrosal nerve within the pterygoid canal containing the cartilaginous substance, which fills the foramen lacerum.

### Nuclei of the cranial nerves

Cranial Nerve	Site of Nucleus
Ist and 2 <sup>nd</sup>	Directly goes to the cerebral cortex
3 <sup>rd</sup> and 4 <sup>th</sup>	Midbrain Cerebral cortex
5 <sup>th</sup> , 6 <sup>th</sup> , 7 <sup>th</sup> and 8 <sup>th</sup>	Pons
9 <sup>th</sup> , 10 <sup>th</sup> , 11 <sup>th</sup> , 12 <sup>th</sup>	Medulla oblongata

### Chapter 5

Head And Neck

### **Cranial Nerve Nuclei**

### 1) Solitary nucleus:

- A series of purely sensory nuclei
- The solitary nucleus receives the axon of all general and special visceral afferent fibers carried into the CN---7,9,10

### 2) Nucleus ambiguous

- A group of large motor neurons, situated deep in the Medullary reticular formation
- Axon arising from cells in this nucleus course in the 9<sup>th</sup> and 10<sup>th</sup> cranial nerve
- The component to the 9<sup>th</sup> nerve is insignificant
- In the 10<sup>th</sup> nerve, these fibers supply the muscle of the soft palate, larynx, pharynx and upper esophagus

### Olfactory Nerve (CN 1)

- It provides special visceral afferent fibers for the smell
- It connects to the brain (not the brainstem!)
- Pass through Perforations in the cribriform plate of the ethmoid bone
- Activate G-protein and is Bipolar nerve
- Pass to the cerebral cortex without going through the thalamus (Bypass thalamus), the only type
  of sensory information that reaches the cerebral cortex directly
- Olfactory receptors → olfactory bulb of the cerebrum →olfactory tract →olfactory cortex,
   hypothalamus and limbic system
- The only neuron that can regenerate, replaced by stem cell
- These are unmyelinated C-fiber, smallest and slowest fiber
- Mitral cell are present in the olfactory bulb
- Olfactory epithelium contains Bowman glands
- Olfactory epithelium possesses non-ciliated epithelium which acts as a receptor for odor
- Sharp order have the quality of water and lipid solubility
- Olfactory area-----anterior perforating substance
- Kallmann syndrome: characterized by hypogonadotropic hypogonadism and Anosmia

## Trigeminal Nerve (CN V)

: -----Trigeminal Nuclei—4-----:

### 1) Motor nucleus-----Pons:

- The motor nucleus is located in the Pons just medial to the main sensory nucleus of the trigeminal
- These motor fibers supply the muscle of mastication

### 2) Main sensory nucleus-----Pons

- The main sensory nucleus is located just lateral to the motor nucleus
- The main sensory nucleus receives tactile and pressure sensation from the face, scalp, oral cavity, nasal cavity and dura
- 3) Spinal trigeminal nucleus: spinal cord to Pons:
  - It is the caudal continuation of the main sensory nucleus

### 4) Mesencephalic nucleus: Midbrain

- The Mesencephalic nucleus is located in the point of entry of the 5<sup>th</sup> nerve and extends
- It receives proprioceptive input from joints, muscle of mastication, Extraocular muscle,
- Some of these fibers synapse monosynapticaly on the motorneurons, forming the sensory
  - limb of the jaw jerk reflex.
- Lesion of Mesencephalic nucleus will result in diminished jaw jerk reflex

: -----Trigeminal Nerve Division—3-----:

### i. Mandibular Nerve

- The mandibular nerve is the largest of the three divisions of the trigeminal nerve
- All branches of the mandibular nerve originate in the infratemporal fossa.
- It is both motor and sensory

- 1) Main trunk
  - Meningeal branch
  - Nerve to medial pterygoid muscle
- 2) Anterior division
  - Masseter nerve
  - Deep temporal nerve
  - Nerve to lateral pterygoid
  - Buccal nerve
- 3) Posterior division
  - Auriculotemporal nerve
  - Lingual nerve:

THE RESERVE THE RE

- ✓ It originates in the infratemporal fossa and passes anteriorly into the floor of the oral cavity by passing through the gap between the Mylohyoid, superior constrictor, and middle constrictor muscles. As it travels through the gap, it passes immediately inferior to the attachment of superior constrictor to the mandible and continues forward on the medial surface of the mandible adjacent to the last molar tooth and deep to the gingiva. In this position, the nerve can be palpated against the bone by placing a finger into the oral cavity.
- ✓ Joined by Chorda tympani and supply anterior 2/3<sup>rd</sup> of tongue
- ✓ Also give pre-ganglionic secretomotor fiber to submandibular gland
- Inferior alveolar nerve-lies in the mandibular canal
- Mylohyoid nerve: branch of inferior alveolar nerve which supplies Anterior belly of digastric muscle

### ii. Maxillary Nerve

- Pain between eyes, lips and the auricular area is carried by maxillary nerve
- The maxillary nerve supplies the skin on the posterior part of the side of the nose, the lower eyelid, the cheek, the upper lip, and the lateral side of the orbital opening.
- The maxillary sinus is supplied by the superior alveolar nerve and the infraorbital nerve

### Chapter 5

**Head And Neck** 

#### Branches

- ✓ In the cranium:
  - ✓ Middle meningeal nerve
- ✓ From the pterygopalatine fossa:
  - ✓ Zygomaticofacial nerve: It supplies the skin over the prominence of the cheek
  - ✓ Zygomaticotemporal nerve:
  - Nasopalatine nerve-----through the Sphenopalatine nerve
  - Greater and lesser Palatine
  - Posterior superior alveolar nerve
  - ✓ Pharyngeal nerve
- ✓ In the infraorbital nerve:
  - o Anterior superior alveolar nerve, Middle superior alveolar nerve
  - o The Infraorbital nerve is a direct continuation of the maxillary nerve. It immediately divides into numerous small branches, which radiate out from the foramen and supply the skin of the lower eyelid and cheek, the side of the nose and the upper lip
- ✓ On the face:
  - o Inferior Palpebral nerve
  - o Superior labial nerve
  - Lateral nasal nerve

### iii. Ophthalmic Nerve

- The ophthalmic nerve supplies the skin of the forehead, the upper eyelid, the conjunctiva, and the side of the nose down to and including the tip. Five branches of the nerve pass to the skin
- The lacrimal nerve supplies the skin and conjunctiva of the lateral part of the upper eyelid
- The infra trochlear nerve
- The external nasal nerve: It supplies the skin on the side of the nose down as far as the tip
- Frontal nerve:
  - ✓ The supraorbital nerve: It divides into branches that supply the skin and conjunctiva on the central part of the upper eyelid; it also supplies the skin of the forehead and the mucous membrane of the frontal air sinus
  - ✓ The supratrochlear nerve: supply the skin and conjunctiva on the medial part of the upper eyelid and the skin over the lower part of the forehead, close to the median plane
- Nasociliary nerve:
  - ✓ The nasociliary nerve arises from the ophthalmic division of the trigeminal nerve
  - Branches:
    - The communicating branch to the ciliary ganglion is a sensory nerve
    - o Long ciliary nerves
    - Posterior ethmoidal nerve
    - o Infratrochlear nerve
    - o Anterior ethmoidal nerve
- Clinical Notes: Herpes zoster Opthalmicus (HZO), also known as ophthalmic zoster, is shingles involving the eye. Symptoms generally include a rash of the forehead with swelling of the eyelid. There may also be eye pain, eye redness, and light sensitivity. Before the rash appears tingling may occur in the forehead along with a fever. The underlying mechanism involves a reactivation of the varicella zoster virus within the ophthalmic nerve.

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NAME AND ADDRESS OF TAXABLE PARTY.

Head And Neck

### Facial Nerve (CN VII)

### **Branches and Course**

1) Course: Begin at the fundus of internal auditory canal, terminate at the stylomastoid foramen

### 2) In facial canal/intracranial: CNG

- Chorda tympani: The Chorda tympani nerve exits the skull and enters the infratemporal fossa through the medial end of the petrotympanic fissure.
- Nerve to the stapedus: Paralysis cause Ipsilateral Hyperacusis (Hypersensitive to sound)
- Greater Petrosal nerve: lesion cause ipsilateral reduce lacrimal fluid production
- Clinical note:
  - Lesion to the facial nerve in the facial canal will cause facial deviation along with loss of sensation from anterior 2/3 of tongue
  - ✓ The facial canal is the longest bony canal of any nerve

### 3) At stylomastoid foramen/Extracranial:

- Posterior auricular muscle-----Ist extracranial branch of the facial nerve
- Posterior belly of digastric muscle
- Stylohyoid muscle

### 4) In face: Two Zebra Bite my Cat

- Temporal
- Zygomatic—Supply orbicularis occuli (medial Palpebral ligament attach to it)
- Buccal
- Marginal mandibular
- Cervical----Supply platysma

#### **Clinical Pearls**

- . Internal auditory meatus content: Facial nerve and vestibulocochlear nerve
- \* Facial nerve enter temporal lobe through this internal auditory meatus
- The facial nerve form internal jenu
- Ramsay Hunt syndrome (herpes zoster oticus) occurs when a shingles outbreak affects the facial nerve near one of your ears.

- Lower one-third of pons contains; facial nucleus
- Crocodile tear syndrome/Bogorad's syndrome: Spontaneous tearing in parallel with the normal salivation of eating. The crocodile tears syndrome occurs most often following facial paralysis when nerve fibers destined for a salivary gland are damaged and by mistake regrow into a tear gland. Caused by facial nerve lesion proximal to the Geniculate ganglion
- The cervical branch of the facial nerve innervate the lower lip through the marginal mandibular branch of the nerve

### **Facial Nerve Paralysis**

Most commonly affect the muscle of facial expression, lacrimation (dry eye), corneal reflex (cant blink), the taste of anterior 2/3 of the tongue and sound damping (Hyperacusis)

The most common cause of unilateral congenital facial palsy is birth trauma related to a difficult delivery. Risk factors include forceps delivery, birth weight of more than 3500 gm and primiparity

On physical examination, forehead involvement should be assessed by asking the patient to raise the eyebrows

- Causes of facial nerve paralysis:
  - Supra-nuclear----UMN = forehead is normal = can wrinkle
    - ✓ Infarct to the face area of motor cortex homunculus (MCA)
    - Infarct to the internal capsule (lacunar stroke)
    - ✓ Infarct to pons (CN VII nucleus)
  - Infra-nuclear---LMN = forehead is paralyzed = No wrinkle
    - ✓ Bell-palsy (linked to HSV so treated with steroids and acyclovir)
    - ✓ Lyme disease -----bilateral facial palsy
    - GBS-----bilateral facial palsy
    - ✓ Herpes zoster oticus----Ramsay-Hunt syndrome---unilateral facial palsy-----------external auditory canal defect and ear pain
    - Sarcoidosis, tumor(acoustic neuroma) and DM

### **Common Facial Expressions**

- Surprise-----Frontalis
- Doubt------Mentalis
- Horror, terror, and fight-----Platysma
- Smiling and laughing------Zygomatic major
- Contempt-----Zygomatic minor
- Grief-----depressor anguli oris
- Anger------Dilator naris and depressor septi

### Glossopharyngeal Nerve (CN IX)

- CN IX is the Glossopharyngeal nerve
- It originates in the medulla oblongata
- It draws fibers from the solitary nucleus (taste) and nucleus ambiguous (motor)
- It draws more fibers from the inferior salivatory nucleus (parotid gland) and dorsal motor nucleus (DMX; pharyngeal sensation)
- It passes through the jugular foramen

## Vagus Nerve (CN X)

- Vagus nerve is the longest cranial nerve
- Cranial Nerve with Longest Extra-Cranial Course
- Pass posteriorly within carotid sheath between IJV and ICA
- Bilateral cutting of vagus nerve cause death
- The vagus nerve provides 75% of all parasympathetic outflow
- 80% of the vagus nerve fiber deliver information from the enteric nervous system (the second brain in Gut) to the brain
- Vagus nerve and thoracic sympathetic nerve end in transverse two third and lateral one-third junctions.
- Posterior to the root of the lung
- Dorsal nucleus of vagus is the major parasympathetic nucleus lies lateral to rhomboid fossa or sulcus limitans means lies in the upper medulla anterior to the floor of 4th ventricle
- If the Vagus nerve cut proximally, the stimulation of the central part will causes apnea

### Accessory Nerve (CN XI)

- It originates in the medulla oblongata and superior cervical cord region
- Supplies:
  - ✓ Trapezius (powerful elevator of scapula) and sternocleidomastoid
- Clinical notes:
  - ✓ The accessory nerve can be evaluated by testing the function of the trapezius muscle. This is most easily done by asking patients to shrug their shoulders against resistance.

### **Cervical Plexus**

- . The cervical plexus is formed by the anterior rami of cervical nerves C2 to C4, and possibly a contribution from the anterior ramus of cervical nerve C1
- . The cervical plexus forms in the substance of the muscles making up the floor of the posterior triangle within the Prevetebral layer of cervical fascia, and consists of:
  - Muscular (or deep) branches;
  - Cutaneous (or superficial) branches

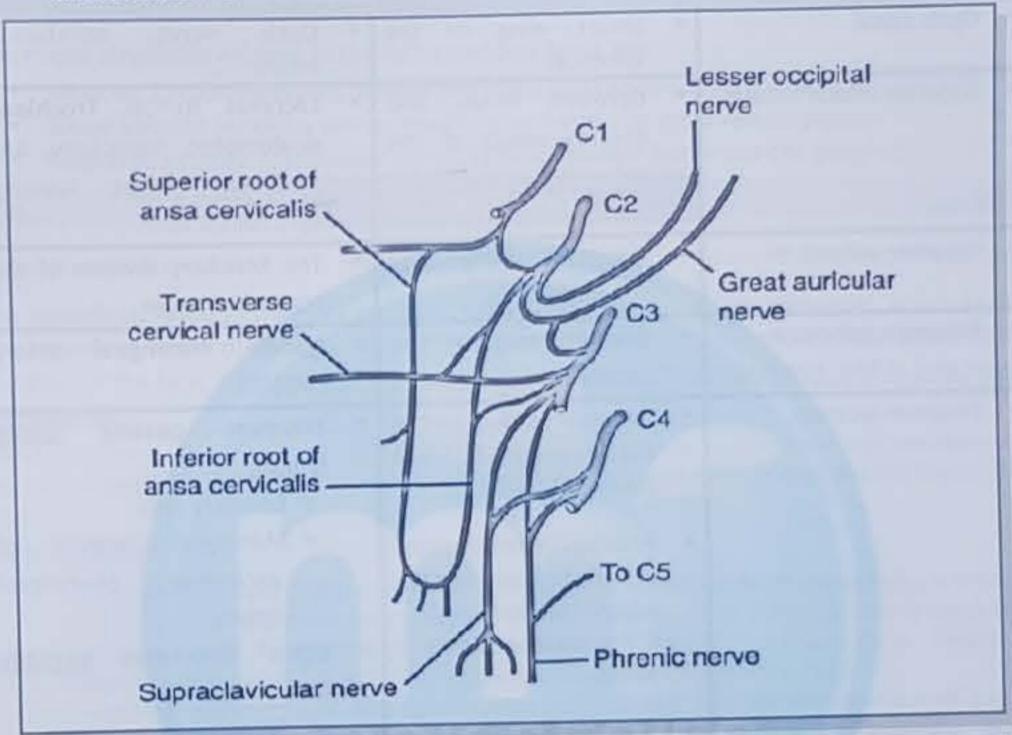
### Muscular (or deep) branches:

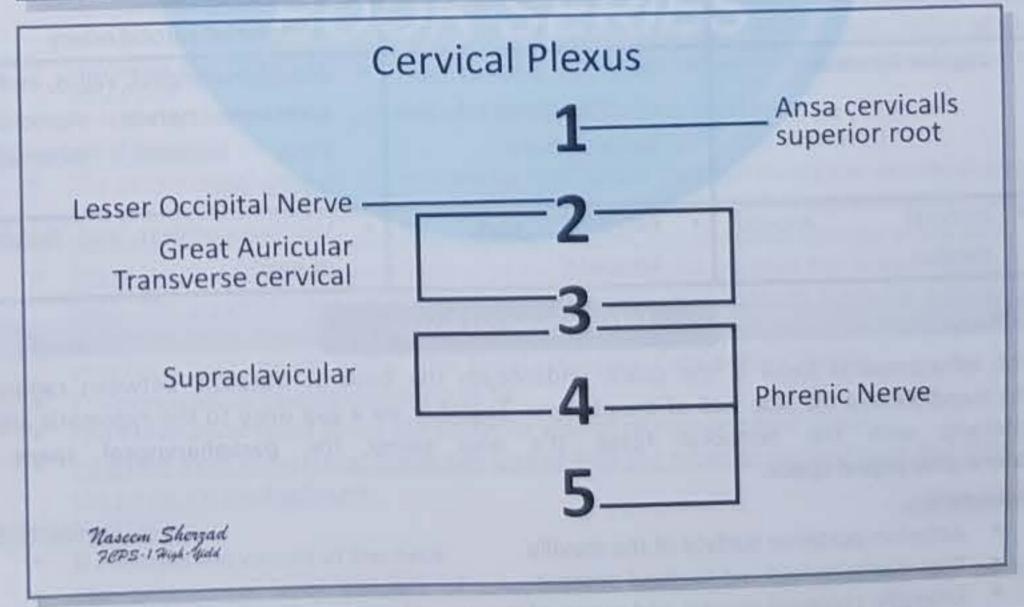
- Several muscular branches of the cervical plexus supply prevertebral and lateral vertebral muscles, including the rectus capitis anterior, rectus capitis lateralis, longus colli, and longus capitis
- Cutaneous (superficial) branches of the cervical plexus are visible in the posterior triangle as they pass outward from the posterior border of the sternocleidomastoid muscle
  - The lesser occipital nerve consists of contributions from cervical nerve C2. Supplies the back scalp and auricle
  - The great auricular nerve consists of branches from cervical nerves C2 and C3. Supplies the angle of mandible
  - The transverse cervical nerve consists of branches from the cervical nerves C2 and C3
  - The supraclavicular nerves are a group of cutaneous nerves from cervical nerves C3 and C4 that, after emerging from beneath the posterior border of the Sternocleidomastoid muscle, descend and supply the skin over the clavicle and shoulder as far inferiorly as rib
  - Greater occipital nerve ——it is the branch of the posterior/dorsal ramus of the 2<sup>nd</sup> cervical nerve. It supplies the scalp as far forward as the vertex of the skull

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**Head And Neck** 

- Ansa (Loop) Cervicalis: it is a nervous loop situated in front of the carotid sheath. It formed by the union of two limb
  - Superior limb: descending from hypoglossal nerve and containing fibers of C1 spinal nerve
  - Inferior limb: from C2 and C3





## **Head And Neck**

# Opening in the base of the skull

Opening in Skull	Bone of Skull Structures Transmitted
Optic canal	<ul> <li>Lesser wing of the sphenoid</li> <li>Optic nerve, ophthalmic artery</li> </ul>
Superior orbital fissure	<ul> <li>Between lesser and greater wings of the sphenoid</li> <li>Lacrimal, frontal, Trochlear, oculomotor, nasociliary, and Abducent nerves; superior ophthalmic vein</li> </ul>
Foramen rotundum	<ul> <li>Greater wing of The Maxillary division of the trigeminal nerve</li> </ul>
Foramen spinosum	<ul> <li>Greater wing of the sphenoid</li> <li>Middle meningeal artery</li> <li>(MS)</li> </ul>
Foramen lacerum	■ Between petrous part of the temporal and sphenoid ■ Structure passing whole length:  ✓ Emissary vein
	<ul> <li>Foramen Cecum Contents:         <ul> <li>1. Nasal emissary vein (to superior sagittal Sinus)</li> <li>2. Prolongation of dura Matter.</li> </ul> </li> <li>Meningeal branch of ascending pharyngeal artery</li> <li>Other structures partially traversing</li> <li>✓ Greater petrosal nerve</li> <li>✓ Internal carotid artery</li> </ul>
Jugular foramen	<ul> <li>Between petrous part of the temporal and occipital bone</li> <li>Glossopharyngeal, vagus, and accessory nerves; sigmoid sinus becomes internal jugular vein</li> </ul>
Internal acoustic     meatus	Petrous part of Vestibulocochlear and facial nerves

### **Infratemporal Fossa**

The infratemporal fossa is the space underneath the base of the skull, between ramus of the mandible and the side wall of the pharynx. Together via a gap deep to the zygomatic arch it interacts with the temporal fossa. It's also called the parapharyngeal space or

### Boundaries:

- Anterior: posterior surface of the maxilla
- Posteriorly: styloid and mastoid process
- Laterally: coronoid process and ramus of the mandible

### Chapter 5

**Head And Neck** 

- Medially: lateral pterygoid plate
- The floor of the infratemporal fossa is comprised of the medial pterygoid muscle, while the roof is formed by the greater wing of the sphenoid bone.
- Two foramina open out on the roof the foramen ovale and foramen spinosum. They provide a connection with the cranial cavity.

### The major structures existing in the infratemporal fossa are:

- Muscles: Lateral pterygoid, medial pterygoid and tendon of Temporalis
- Blood vessels: Maxillary artery, maxillary vein and pterygoid venous plexus
- Neural structures: Mandibular nerve, Chorda tympani nerve and otic ganglion

### Cervical Fascia



#### Superficial cervical fascia

The superficial fascia in the neck contains a thin sheet of muscle (the platysma), which begins in the superficial fascia of the thorax, runs upwards to attach to the mandible and blend with the muscles on the face, is innervated by the cervical branch of the facial nerve and is only found in this location.

### Deep cervical fascia

Deep to the superficial fascia, the deep cervical fascia is organized into several distinct layers. These include:

### 1) Investing layer:

- The superficial layer of the deep cervical fascia, also known as the investing layer, is the one of three layers of the deep cervical fascia that surrounds all of the neck that is deep to the platysma. The layer includes the Masticator fascia, submandibular fascia and sternocleidomastoid-Trapezius fascia. Surrounds all structures in the neck
- Attaching posteriorly to the ligamentum nuchae and the spinous process of the CVII vertebra, this facial layer splits as it passes forward to enclose the trapezius muscle, reunites into a single layer as it forms the roof of the posterior triangle, splits again to surround the sternocleidomastoid muscle, and reunites again to join its twin from the other side.
- Anteriorly, the investing fascia surrounds the infrahyoid muscles.

### 2) Prevertebral layer:

- The prevertebral layer is a cylindrical layer of fascia that surrounds the vertebral column and the muscles associated with it. Muscles in this group include the prevertebral muscles, the anterior, middle, and posterior scalene muscles, and the deep muscles of the back.
- There is one additional specialization of the prevertebral fascia in the lower region of the neck. The prevertebral fascia in an anterolateral position extends from the anterior and middle scalene muscles to surround the brachial plexus and subclavian artery as these structures pass into the axilla. This facial extension is the axillary sheath.
- The prevertebral fascia extends up to T4
- The Prevetebral fascia forms the posterior wall of retropharyngeal space
- Infection from Prevetebral fascia can spread into the superior mediastinum and then into the posterior mediastinum

### 3) Pretracheal layer:

- It encloses the viscera of the neck
- The pretracheal layer consists of a collection of fascias that surround the trachea, esophagus, and thyroid gland

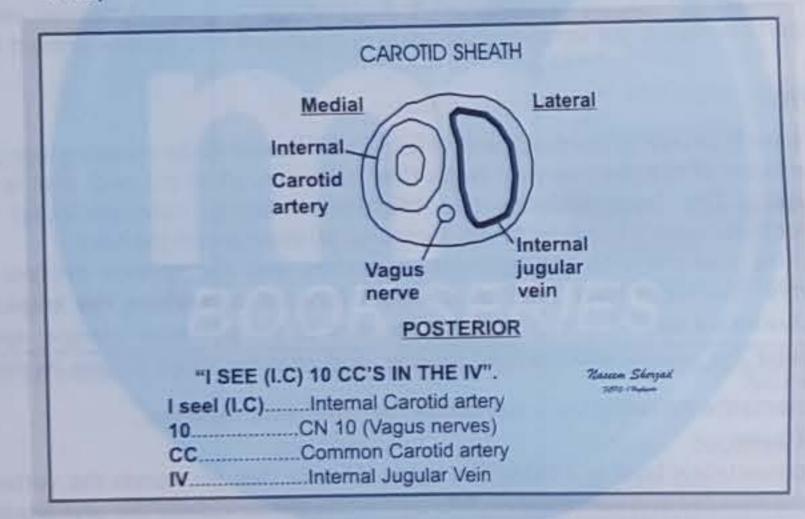
### Chapter 5

#### **Head And Neck**

- Thyroid gland moves with swallowing because it is enclosed in pretracheal tissue Anteriorly, it consists of a pretracheal fascia that crosses the neck, just posterior to the infrahyoid muscles, and covers the trachea and the thyroid gland.
- Posteriorly, the buccopharyngeal fascia forms the pretracheal layer and separates the pharynx and the esophagus from the prevertebral layer
- Pretracheal fascia infection can spread to the anterior mediastinum

### 4) Carotid sheaths:

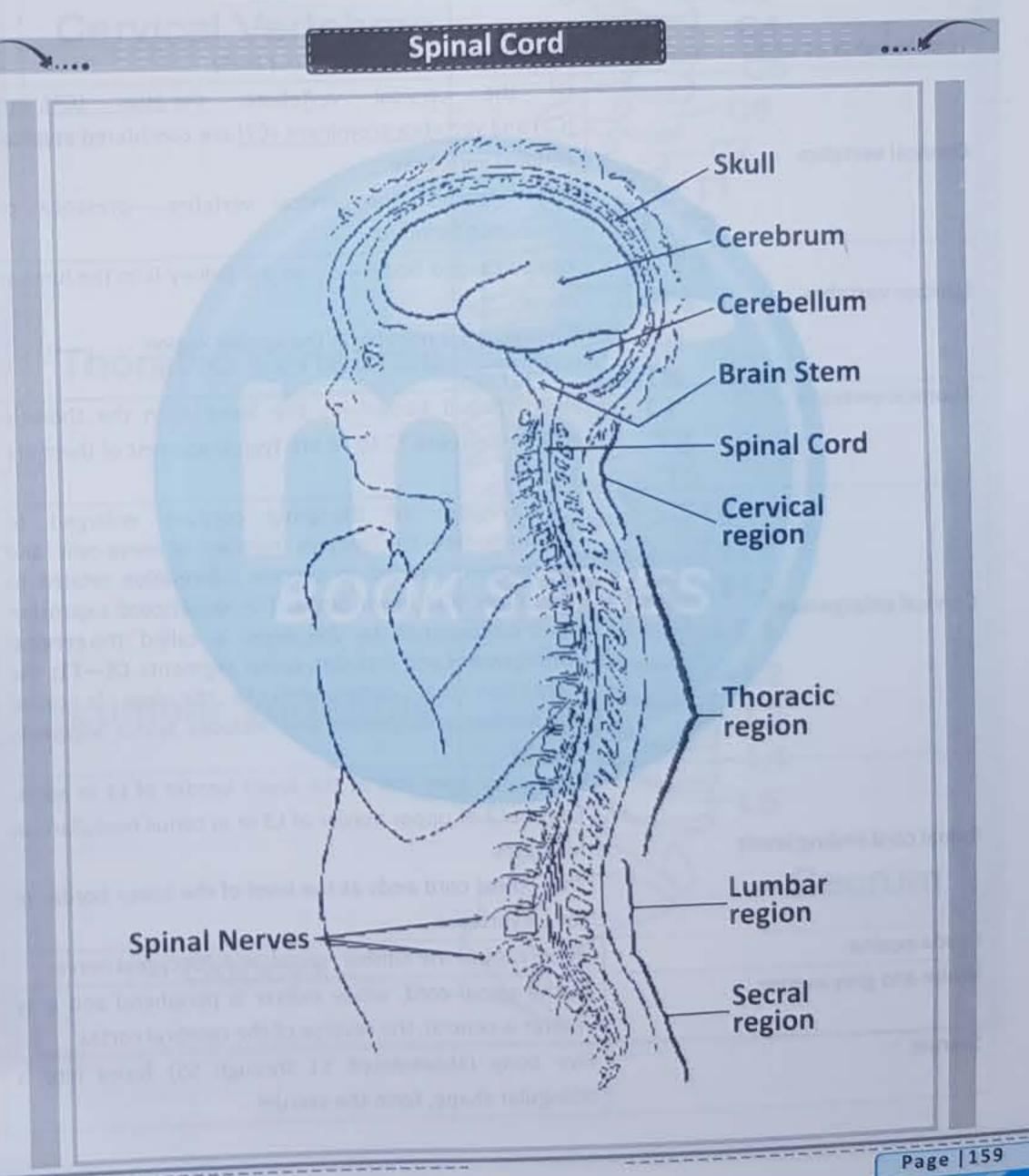
- Which receives a contribution from the other three facial layers and surrounds the two major neurovascular bundles on either side of the neck.
- It Blends with the deep part of the parotid fascia
- It receives contributions from the investing, prevertebral, and pretracheal layers, though the extent of each component's contribution varies
- Content: I see 10 CC,s in the IV
  - Lateral----Internal Jugular Vein
  - Medial----CCA and ICA
  - ✓ Lies in between two structure(artery and vein) but in posterior plan--- CN 10 (vagus nerve)



### **Naseem Sherzad High-Yield Points**

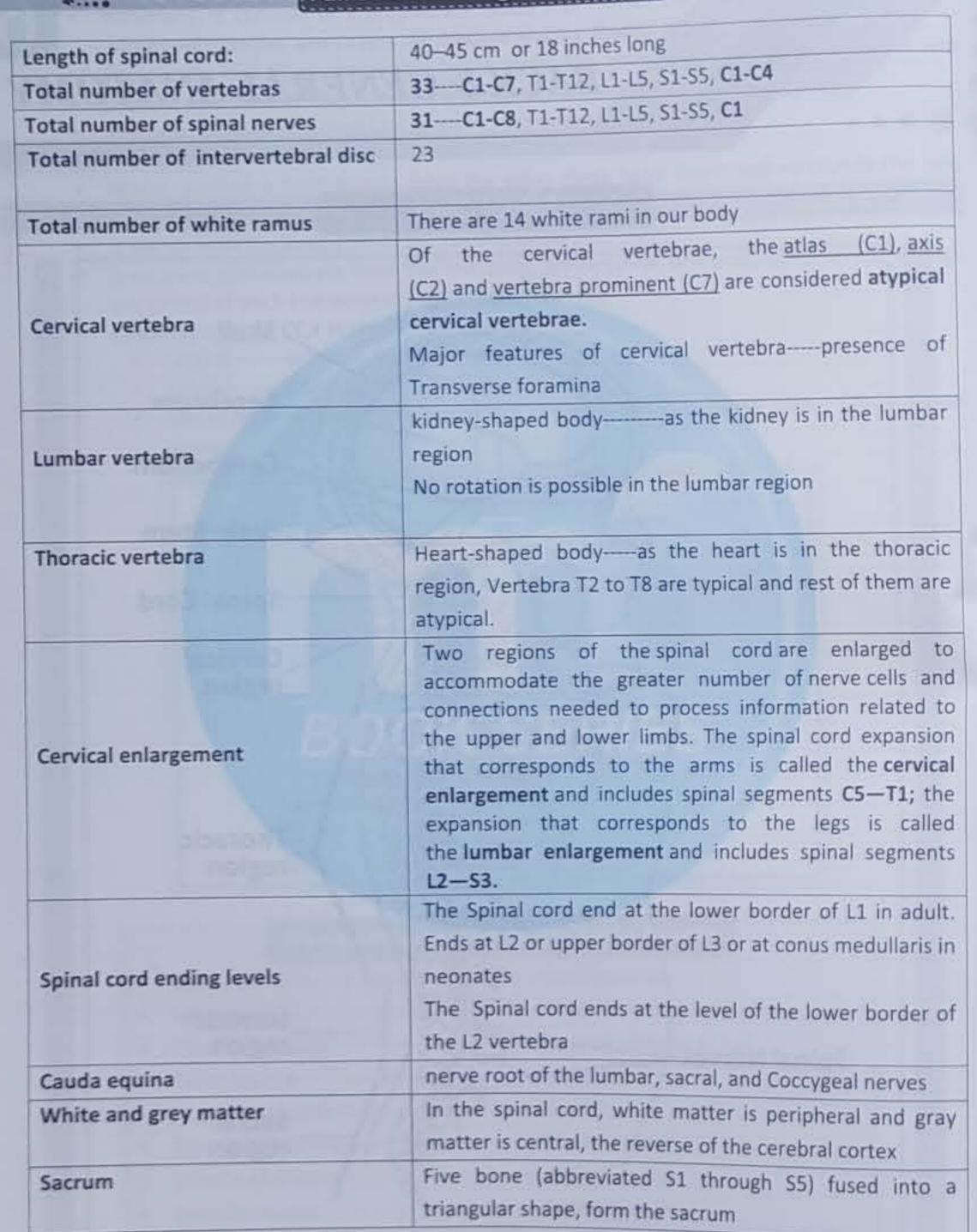
- Safety or lifesaving muscle of tongue—Genioglossus
- safety muscle of the larynx-----Posterior cricoarytenoid muscle
- -Superior oblique of eye Cheating muscle---
- Tailor muscle--Sartorius
- -Gracilis Anti-rape muscle-
- -Medial rectus Muscle of marriage-
- -Lateral rectus Muscle of divorce-
- -Serratus anterior Boxer's muscle-

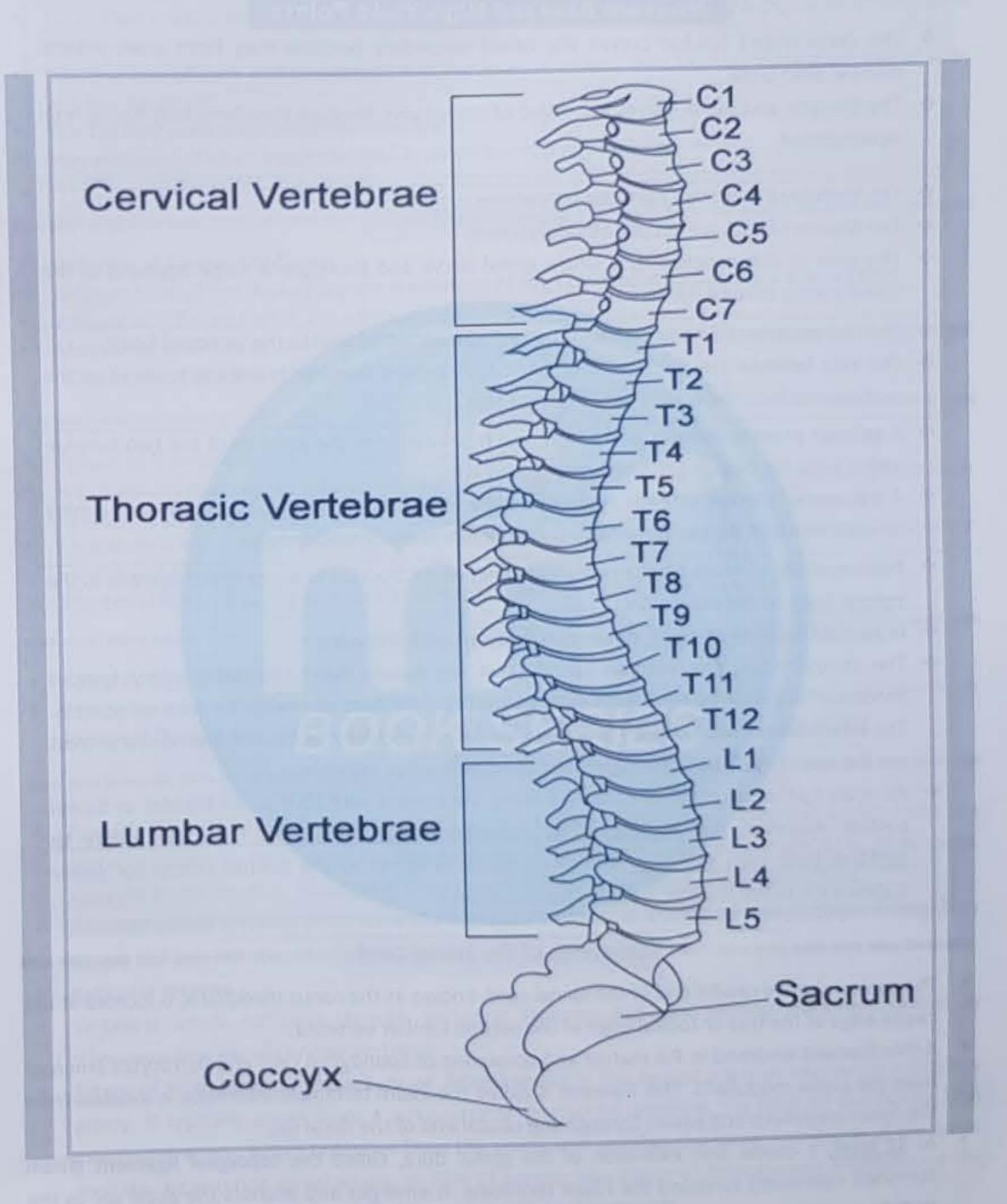
# CHAPTER BACK & GENERAL ANATOMY



Chapter 6

### Full detail and High Yield Points





## **Back And General Anatomy**

### Chapter 6

Naseem Sherzad High-Yield Points

- The cervical and lumbar curves are called secondary because they form later, several
- ❖ The thoracic and sacral curves are called primary curve because they form first during fetal development
- The Vertebrae is derived from the sclerotome
- The Muscle of back are supplied by dorsal rami
- The area of skin supplied by a single spinal nerve and therefore a single segment of the
- The two pedicles are bony pillars that attach the vertebral arch to the vertebral body;
- The two laminae are flat sheets of bone that extend from each pedicle to meet in the midline and form the roof of the vertebral arch.
- ❖ A spinous process projects posteriorly and inferiorly from the junction of the two laminae and is a site for muscle and ligament attachment.
- A transverse process extends posterolaterally from the junction of the pedicle and lamina on each side and is a site for articulation with ribs in the thoracic region.
- Poliomyelitis: it results from a relatively selective destruction of lower motorneurons in the ventral horn by the polio virus
- In suicidal hanging attempt, death occurs by arterial occlusion
- \* The central ridge, the median sacral crest represents the fused rudimentary spinous process of superior three or four sacral vertebrae; S5 does not have the spinous process. The intermediate sacral crest represents the fused articular process and lateral sacral crest are the tips of the transverse process of the fused sacral vertebra
- An injury to the sacral spinal cord may leave the patient with little or no bladder or bowel control, however, the patient will be completely autonomous and have the ability to perform their own self-care. The sacral region is home to the control center for pelvic organs such as the bladder, bowel, and sex organs.

### Coverings of the Spinal Cord

- NAME AND ADDRESS OF REAL PROPERTY. The conical-shaped caudal end of the spinal cord, known as the conus medullaris, is located at the caudal edge of the first or rostral edge of the second lumbar vertebra
- A thin filament enclosed in Pia matter and consisting of Ependymal cells and Astrocytes emerges from the conus medullaris. This filament is called the Filum terminale internum. It extends from the conus medullaris and passes through the caudal end of the dural sac.
- . At S2 level, a caudal thin extension of the spinal dura, called the coccygeal ligament (Filum terminale externum) surround the Filum terminale. It emerges and anchors the dural sac to the vertebral canal

### Syringomyelia

- Fluid-filled cavitation within the center of the spinal cord that expands the diameter of the spinal cord
- Bilateral loss of pain and temperature at the level of lesion, "belt-like" or "cape-like" loss of pain and temperature
- The Cervical cord is the most common site
- May present with hydrocephalus and Arnold-Chiari I malformation

#### **Tabes Dorsalis**

Common at lumbar cord level

- Degeneration of the dorsal/posterior columns of the spinal cord and sensory nerve roots
- Present with Paraesthesia, Pain, Polyuria-----3Ps
- Associated with late or tertiary stage syphilis, sensory ataxia, positive Romberg sign, suppressed reflexes and Argyll Robertson pupil

#### Sacral Hiatus

- Failure of fusion of lamina of 4<sup>th</sup> and 5<sup>th</sup> sacral vertebra
- It is surrounded on either side by sacral cornua, that are of great importance for the identification of sacral hiatus on the body surface
- Caudal epidural injections used to treat sacral and lower lumbar nerve root impingement occur via the sacral hiatus.
- The sacral hiatus is partly or entirely covered by the sacrococcygeal ligament

#### Joints

Sacro-Coccygeal joint-----Symphysis

Sacro-iliac joint-----type, anteriorly synovial and posteriorly Syndesmoses. Subtype---Plana joint, the blood supply of this joint is from posterior division of the internal iliac artery

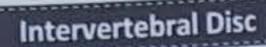
### Blood supply of spinal cord: -----Vertebral arteries

- Posterior spinal arteries: The posterior spinal artery (dorsal spinal arteries) arises from the vertebral artery in 25% cases or the posterior inferior cerebellar artery (PICA) in 75% cases, adjacent to the medulla oblongata. They supply the posterior third of the spinal cord.
- Anterior spinal arteries: Arise from the vertebral arteries and unite to form a single artery. They supply the anterior two-third of the spinal cord
- Reticular arteries

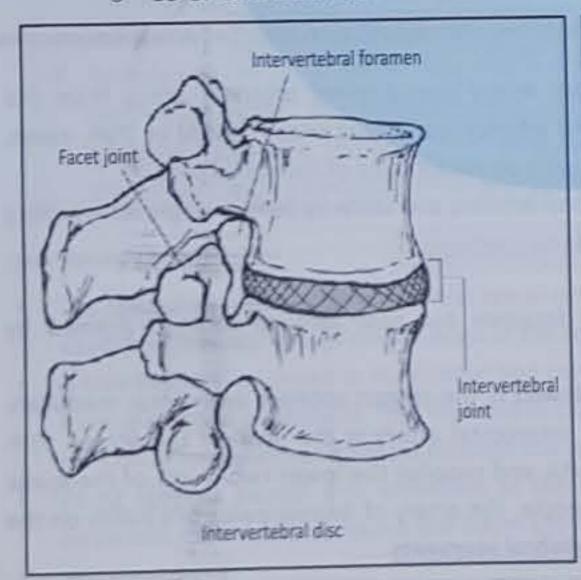
- Vertebral artery not pass through vertebral foramen but pass through foramen formed by transverse process of cervical vertebra
- Artery of Adamkiewicz: The artery of Adamkiewicz is the largest anterior segmental medullary artery. It typically arises from a left posterior intercostal artery at the level of the 9th to 12th intercostal artery, which branches from the aorta, and supplies the lower two-thirds of the spinal cord via the anterior spinal artery. In 75% of people, the artery of Adamkiewicz originates on the left side of the aorta between the T8 and L1 vertebral segments

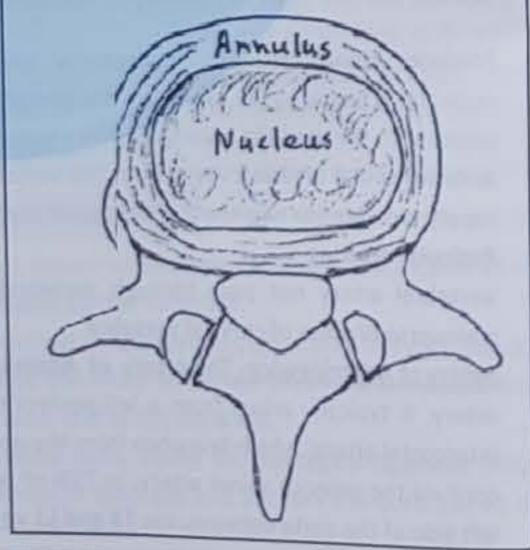
**Back And General Anatomy** 

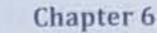
**Back And General Anatomy** 



- Intervertebral disc exhibit a great deal of strength because of the presence of thick bundle of collagen fiber of Fibrocartilage
- It is Avascular structure and nutrient diffuse through endplate
- The discs are thinnest in the thoracic region and thickest in the lumbar region.
- Each disc contains an annulus fibrosus (outer ring) and nucleus pulposus (inner gel-like substance)
- There are at least 23 Intervertebral discs interposed between the vertebral bodies
- No Intervertebral disc found between the first and 2<sup>nd</sup> cervical vertebra (C1-C2) or in the sacrum or coccyx
- The discs account for approximately one-quarter (1/4th or 25%) of the total length of the vertebral column, and are primarily responsible for the presence of the various curvatures
- The Fracture can occur anywhere along the spine. Five to ten percent occur in the cervical region (neck). Sixty-four percent occur in the Thoracolumbar region, often at T12-L1
- Herniation:
  - √ 95% involve L4-L5 and L5-S1
  - ✓ The Posterio-lateral/paracentral Prolapse is commonest
  - All spinal nerves, except the first, exit below their corresponding vertebrae
  - ✓ In the cervical segments, there are 7 cervical vertebrae and 8 cervical nerves. C1-C7 nerves exit above their vertebrae whereas the C8 nerve exits below the C7 vertebra. It leaves between the C7 vertebra and the first thoracic vertebra. Therefore, each subsequent nerve leaves the cord below the corresponding vertebra.
  - ✓ The herniation disc will usually compress the spinal nerve root one number below the involved disc e.g.
    - o Intervertebral herniation between 5th and 6th cervical vertebral disc will damage C6 spinal nerve root
    - Herniation of Intervertebral disc between L4 and L5 would most likely impinge root of L5

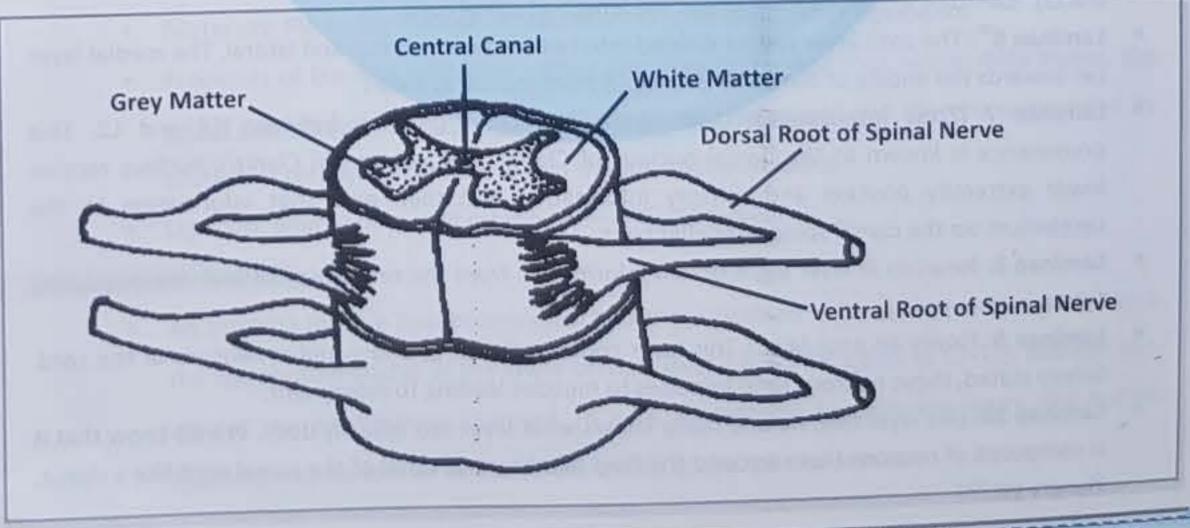






### Spinal Nerve

- Mixed nerve which carry sensory, motor and autonomic signals
- Postganglionic sympathetic fiber are present in all spinal nerve
- There are 31 pairs of spinal nerve
- These nerves are divided into 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 Coccygeal nerve
- Dorsal root (sensory): Afferent, carry sensory information to brain
- Ventral root (Motor): Efferent, carry motor information from brain
- When an anterior and a posterior root unite, they form spinal nerve
- Spinal nerve split into two main branches 1) posterior ramus 2) anterior ramus
- Dorsal and ventral roots enter and leave the vertebral column respectively through Intervertebral foramen at the vertebral segments corresponding to the spinal segment.
- Ventral/anterior ramus: Huge, it innervate so much
- Dorsal/posterior ramus: innervate skin of back, deep back muscles
- Dorsal rami of the cervical nerves innervate-----extensor of trunk
- Dorsal root ganglion:
  - Located in inter vertebral foramen, lies proximal to formation of spinal nerve
  - Pseudo-polar type neuron
  - Synapses Absent in Dorsal root ganglion----SAD
  - Contain all sensory tract, means ascending tract



### **Rexed Laminae**

The Rexed laminae represent a system of organizing the neurons of the spinal cord (they were actually designed to torture medical students, I joke of course, sort of...). They are named after Dr. Bror Rexed who was a Swedish neuroscientist. It is important to note that the Rexed laminae are not strictly organized based on anatomical location, but are actually based on the types, and functions, of the neurons in each laminae

- --- Rexed laminae 1-VI Dorsal Horn----
- Ventral horn------Rexed laminae VIII-IX
- -lamina V11 o Intermediate zone-----

#### Laminae one:

- ✓ Cell respond to noxious stimuli or thermal stimuli
- ✓ Send information to the brain by the contralateral Spinothalamic tract.
- ✓ In general, nociceptors responding to noxious stimuli transmit the information to the CNS via A delta fibers, which make synaptic connections to neurons in Rexed layer I
- √ Correspond to marginal zone
- Laminae two: Layer two, which is also known as the substantia gelatinosa, gets information from the Spinothalamic tract as well as the dorsal columns. The spinothalamic tract relays information about painful stimuli and the dorsal columns relay information about non-painful stimuli. Therefore, the neurons in layer two receive information about both painful and non-painful stimuli.
- Laminae three and four (nucleus proprius): The nucleus proprius, aka layers three and four, receives information from the body about touch and proprioception (hence the name "proprius").
- Lamina 5: Nobody knows exactly what the hell layer five does, but it receives information from a wide variety of sources including pain sensation from the bodies' organs, as well as information about movement from the brain (via the corticospinal tracts) and brainstem (via the rubrospinal tracts). Lamina 4 extended throughout the length of spinal cord.
- Laminae 6th: The sixth layer can be divided into two sections: medial and lateral. The medial layer (ie: towards the middle of the cord) gets input from muscle spindles.
- Laminae 7 (Zona intermedia): Layer seven is most prominent between C8 and L2. This prominence is known as the dorsal nucleus of Clarke. The neurons in Clarke's nucleus receive lower extremity position and sensory information and then pass that information to the cerebellum via the dorsal spinocerebellar tract.
- Laminae 8: Neurons in layer eight obtain information from the reticulospinal and vestibulospinal tracts.
- Laminae 9: Finally an easy layer! This layer contains the a, B, and y motor neurons of the cord. Simply stated, these neurons send impulses to muscles leading to movement.
- Laminae 10: Like layer five, no one really knows what layer ten actually does. We do know that it is composed of neurons that surround the fluid filled central canal of the spinal cord like a donut. Hungry yet???

Chapter 6

**Back And General Anatomy** 

### Spinal Cord Ligament & Covering

### 1) Ligamentum flavum:

- Connect adjacent lamina
- 2) Supraspinatus and infraspinatus ligament:
  - · Connect adjacent spine
  - In the cervical region, Supraspinatus and infraspinatus ligament are greatly thickened and ligamentum nuchae

### 3) Transverse ligament:

Support the odontoid process of the axis on atlas

### 4) Anterior and posterior longitudinal ligament:

- These are primary spine stabilizer
- Both of these ligaments runs the entire length of the spinal cord
- These prevent anterior and posterior dislocation of spinal cord
- These are not punctured during LP
- Ligament that checks hyperextension of vertebral column-----anterior longitudinal ligament
- Ligament affected with whiplash injury------Anterior longitudinal ligament

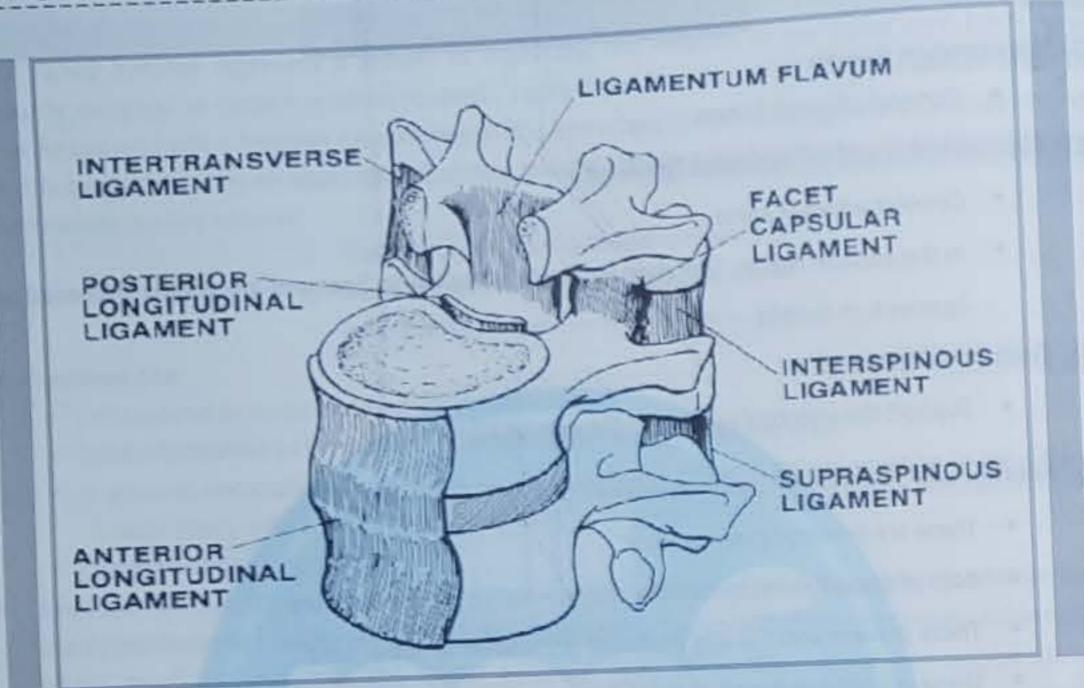
### 5) Denticulate ligament:

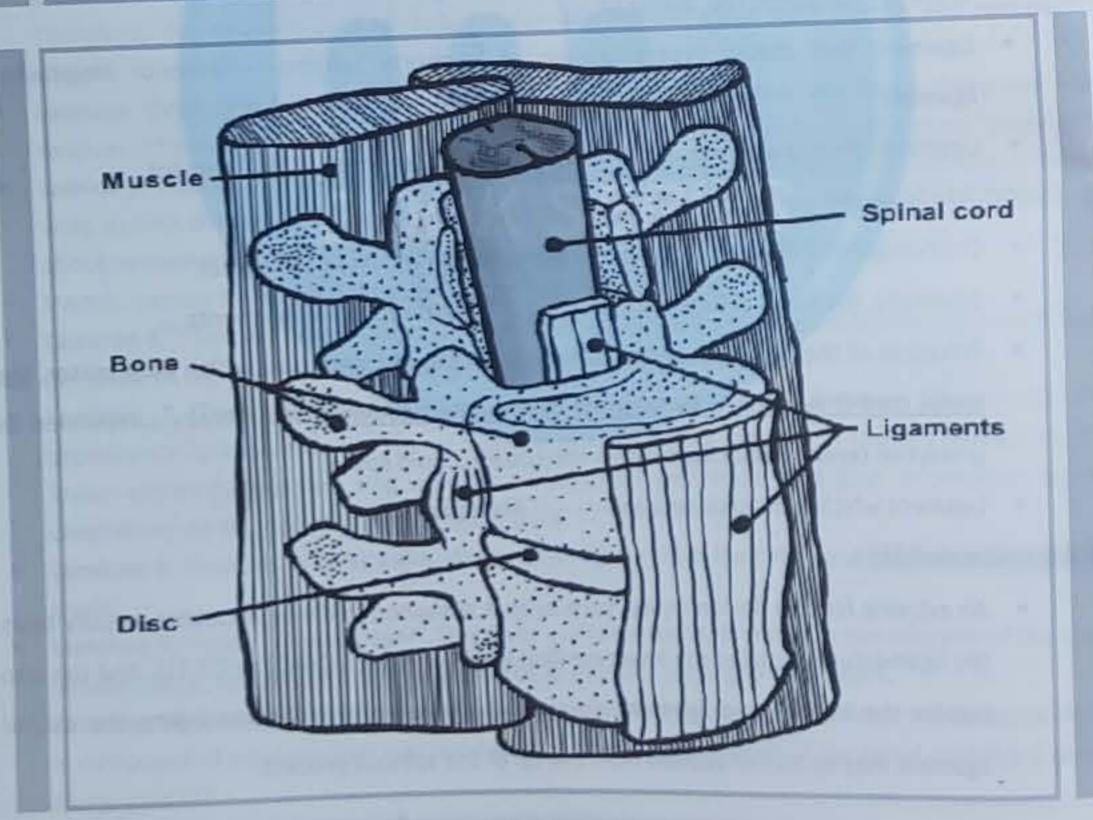
- Condensation of PIA matter and adherent to Arachnoid and dura matter
- Bilaterally, PIA mater collagen is thickened to form denticulate ligaments.
- Processes of the ligaments periodically join dura mater and thus, within dura mater, the spinal cord is suspended by bilateral denticulate ligaments and thereby surrounded by protective cerebrospinal fluid within the subarachnoid space.
- Ligament which limits skull rotation------Alar ligament

### 6) Ligament nuchae:

 An extreme forcible flexion injury, such as that sustained in diving accidents, usually tears the ligamentum nuchal at the lower cervical level (i.e. C5-C6, C6-C7 or C7-T1). And can also involve the interspinous ligament. In such an extreme hyperflexion injury, the nuchal ligament may be torn or avulsed from the tip of the spinous process

Back And General Anatomy





Special Features Of Vertebras

### ....

### C1 (Atlas)

- Nobody, no spinous process
- Only motor, no sensory
- . The Lesion in atlas can cause death
- No posterior cutaneous supply
- Atlanto-occipital joint:
  - ✓ The atlanto-occipital joints are synovial joints that are formed between the occipital condyles, which are found on either side of the foramen magnum above and the facets on the superior surfaces of the lateral masses of the atlas below. They are enclosed by a capsule.
  - ✓ Type synovial joint, subtype: Condyloid joint
  - ✓ "Yes" movement—flexion and extension occur here –say yes
  - ✓ The atlanto-occipital joint allows the head to nod up and down on the vertebral column.
  - ✓ Movement: Flexion, extension, and lateral flexion. No rotation is possible.

### C2

- The Axis (C2 vertebra) also known as epistropheus
- Having strong odontoid process called dens
- Death in hanging is due to fracture of the odontoid process
- Atlanto-axial joint:

- ✓ The atlantoaxial joints are three synovial joints: one is between the odontoid process and the anterior arch of the atlas, and the other two are between the lateral masses of the bones
- ✓ "NO" moment occur here.....say No----right to left head moment will occur
- ✓ Type synovial joint, subtype Pivot joint
- ✓ Rotation is the primary movement
- ✓ Flexion and extension is limited by the tectorial membrane

### C6

- Level of Beginning of esophagus and trachea
- Level of Cricoid cartilage

NAME AND ADDRESS OF TAXABLE PARTY.

- Contain carotid tubercle for Internal carotid artery
- We press C6 to stop bleeding from ICA
- Vertebral artery ascends from here through the foramen of the transverse process

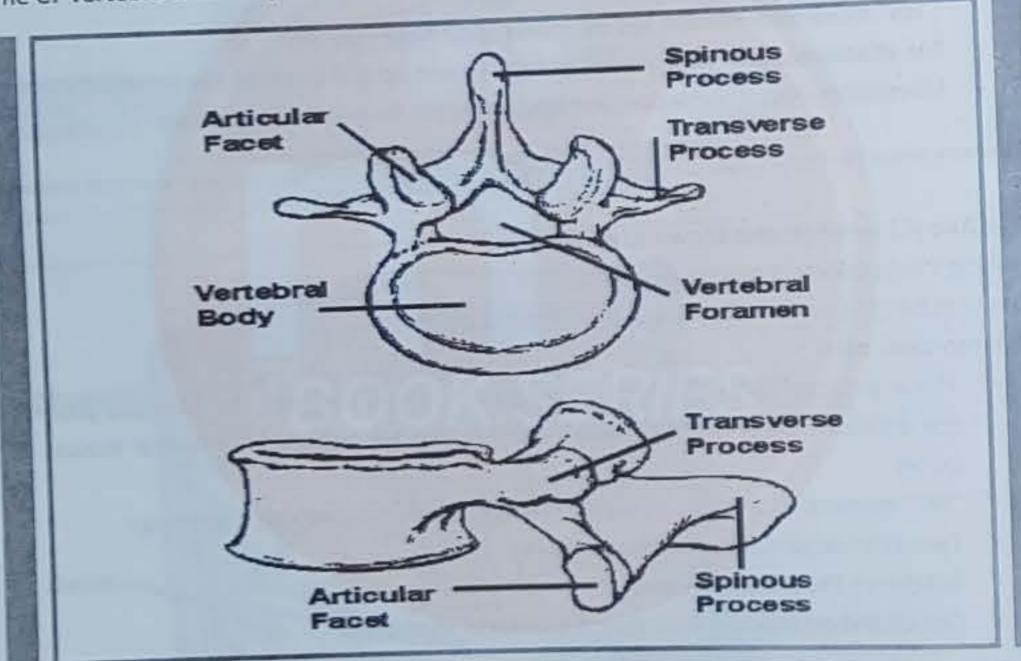
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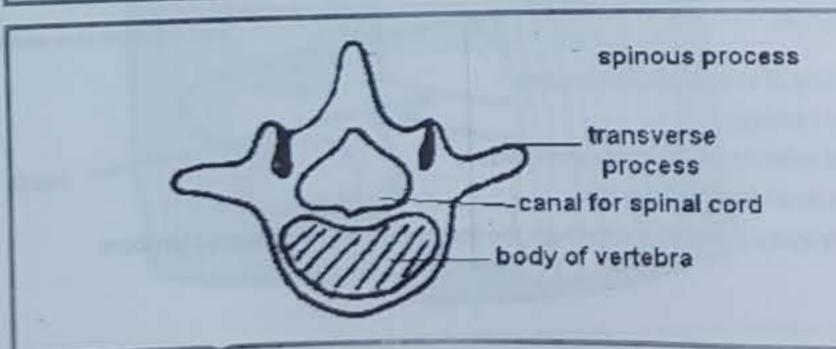
NAME AND ADDRESS OF TAXABLE PARTY.

- A patient can survive without mechanical ventilation if the lesion below C5
- A patient can't survive without mechanical ventilation if the lesion above C5

**C7** 

- Ganglion at C7 is Cervicothoracic ganglion
- Longest spinous process but spinous process not bifed
- Lesion at C7 cause loss of sympathetic tone to heart, as a result, heart rate and abdominal
- The number of cervical vertebrae is constant, but the seventh cervical vertebra may possess a cervical rib
- Prominence vertebra which helps in counting vertebra
- Possess transverse process which is large but not transmitting vertebral artery
- The C7 vertebra is developed from C7-C8 somites





Chapter 6

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### **Back And General Anatomy**

## Some Condition Of Spinal Cord



### 1) Lordosis:

- ✓ Increase in the lumbar and cervical curves of the vertebral column is called Lordosis, Abnormal curvatures in the lumbar region cause Lordosis
- ✓ Posterior is concave and anterior is convex
- ✓ Women produce temporary Lordosis during late pregnancy
- ✓ Loss of posterior curvature in the infant is called Lordosis

### 2) Kyphosis

- ✓ Increase in the thoracic curves of the vertebral column is called kyphosis
- Posterior is convex and anterior is concave
- ✓ Loss of anterior curvature in the infant is called kyphosis.

### 3) Scoliosis:

- ✓ Characterized by an abnormal lateral curvature usually in the thoracic region that is accompanied by rotation of the vertebra
- ✓ This curve is S-shaped or C-shaped. This is the most common deformity in pubertal girl

### 4) Sacralization:

✓ Sacralization leads to fusion of the L5 (fifth lumbar vertebra) and S1 (first sacral vertebra) and the intervertebral disc between them may be narrow.

### **Brown Sequard Syndrome**

### Hallmark:

- . Two ipsilateral sign
  - ✓ Ist -----Loss of all sensation and flaccid weakness at the site of the lesion.
  - √ 2<sup>nd</sup>----ipsilateral loss of sensation below the site of lesion

### · one contralateral sign

- ✓ Contralateral loss of pain and temperature—1-2 segment below the site of lesion
- Hemisection is differentiated from total spinal section by spinal shock
- Right Hemisection of the spinal cord: Patient present with loss of proprioception on right and loss of pain and temperature on the left side

### Complete cord transection:

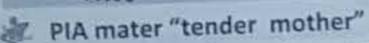
- ✓ All ascending tract from below and descending tract from above are interrupted
- Affect motor, sensory and autonomic functions
- Bilateral lower motor neuron paralysis and muscular atrophy in the segment of the lesion
- Bilateral spastic paralysis below the level of the lesion

### Triangle of Petit

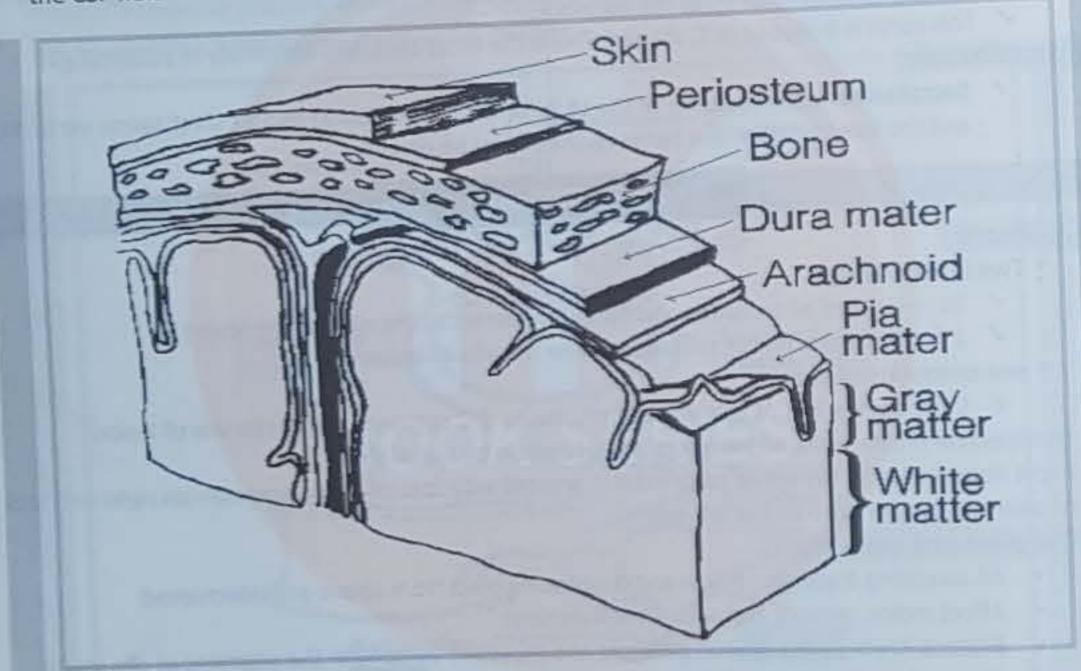
- It is also known as "inferior lumbar triangle"
- Lumbar hernia protrudes from inferior lumbar triangle
- Boundaries
  - √ Inferiorly------Iliac crest
  - Posteriorly------Latissimus Dorsi
  - ✓ Anteriorly-----External oblique
  - √ Floor-----Internal oblique

**Back And General Anatomy** 

Meninges --- I-PAD



- LP Needle cant cross PIA mater, PIA mater extend into sulci and fissures of brain tissue
- Arachnoid mater "spider-like-mother"
  - Avascular
- Dura mater "tough mother"
  - Supplied by all divisions of the trigeminal nerve
  - · Pain sensitive
  - Consist of two-layer
    - √ Periosteal layer
    - ✓ Meningeal layer—Cause division like falx cerebri
- . Leptomeninges: the inner two Meninges the PIA and arachnoid mater, between which circulate the CSF fluid



### Epidural/Extradural hematoma

- . Collection of blood between the dura and skull, the common site is temporal bone
- . CT-scan: lens shaped lesion or biconvex hyperdense lesion
- The Lucid interval may precede neurological sign
- . Hernia is the lethal complication.
- Epidural space contain vertebral venous plexus
- . The anterior branch of the middle meningeal artery runs beneath the pterion. It is vulnerable to injury at this point, where the skull is thin. Rupture of the artery may give rise to an epidural hematoma. In the dry cranium, the middle meningeal, which runs within the dura mater surrounding the brain, make a deep groove in the calvarium

### Important points:

- √ The Epidural space has its widest point (5mm) at----- L2
- ✓ Second sacral vertebra (S2):
  - The epidural space extends from the base of the skull to the end of dural sac at this level
  - Subarachnoid space end at this level
  - The arachnoid extends with the dura down to the level of S2
- ✓ Area of subarachnoid space that are increased in width----- subarachnoid cisterns
- ✓ The Widest part of subarachnoid cisterns-----cisterna magna

- Crescent or sickle-shaped
- . Collection of blood underneath the dura
- It is due to the tearing of bridging veins between dura and arachnoid.

### Superior Cerebral vein:

- ✓ The superior cerebral veins drain the superolateral and medial surfaces of the cerebrum.
- ✓ They ascend, pierce the arachnoid mater, traverse the subdural space and enter the superior sagittal sinus or its lacunae.
- ✓ Traumatic anteroposterior displacement of the cerebral hemispheres may rupture these veins in the subdural cleavage plane, causing a subdural hemorrhage.

### Subarachnoid Hemorrhage

- RBC's are not normally found in the CSF but may be present after the traumatic spinal tap or subarachnoid hemorrhage
- Subarachnoid space:
  - ✓ The subarachnoid space is the interval between the arachnoid membrane and the PIA.
  - Contents: CSF, nerve root and blood vessels that supply the spinal cord
  - ✓ The major arteries and veins of the brain are located in this space

### Causes:

- ✓ Saccular (berry) aneurysm (most common)
- √ Vascular malformation
- ✓ Tumors, Systemic hypertension

### Clinical features:

- ✓ Abrupt onset, intensely painful "thunderclap" headache
- ✓ Often described as the "worst headache of my life"

### Investigation:

- √ Non-contrast CT scan; it is the best initial test
- ✓ Lumbar puncture: it is the investigation of choice
- ✓ LP finding:
  - · Pressure increased
  - Color: Xanthochromia (yellow from RBC hemolysis within CSF)
  - RBC raised
  - WBC and glucose: normal

### a. Treatment:

- ✓ CCB (e.g. Nimodipine)-----to prevent vasospasm
- ✓ Surgical clipping of the aneurysm

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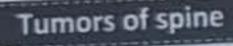
### SPINA BIFIDA

### 1) Spina bifida occulta:

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- Failure of posterior neuropore to close, or to induce bone growth around it.
- Vertebra fail to form around the spinal cord
- This is the mildest form
- No increase in AFP, asymptomatic
- The Tuft of hair over the defect
- 2) Spina bifida with Meningocele:
  - Meninges protrude through the vertebral defect, increase in AFP
- 3) Spina bifida with Meningomyelocele:
  - Meninges and spinal cord protrude through the vertebral defect
- 4) Spina bifida with myeloschisis
  - Most severe
  - The Spinal cord can be seen externally

  - Important to note that Acetylcholine esterase is more specific to the central nervous system, separating open spinal defects from abdominal wall defects, which can also cause elevated AFP level



Tumor of the spine can be metastatic or primary

### Metastatic tumors:

- Account for 98% of all spine lesion
- Common malignancy that metastasizes to the spine are:
  - √ Breast cancer—21%
  - √ Lung cancer ----14%
  - ✓ Prostate----7.5%
  - ✓ Renal-----5%
  - √ Gastrointestinal—5%
- The Common route of metastases are:
  - Embolization through the venous system (Batson's plexus)----most common
  - ✓ Embolization through the arterial system
  - Direct extension
  - √ Lymphatic spread

#### Features:

- √ 80% present with progressive unrelenting pain
- √ 20% present with spinal cord compression
- ✓ Most are sclerotic due to osteoblastic activity (e.g. prostate)
- ✓ Some are Osteolytic due to osteoclastic activity (e.g. renal cell carcinoma)

### Primary tumors:

- These account for 2% of spine lesion
- These are of following types
  - ✓ Bone forming tumor:
    - Myeloma and Osteoma
    - Osteoblastoma

### √ Cartilage forming tumor

- - o Chondroma
  - Osteochondroma
  - Chondrosarcoma
- ✓ Spinal cord tumor
  - o Glioma
  - Ependymoma and Astrocytoma
- Features
  - Benign tumor tends to occur in the posterior elements
  - ✓ Malignant tumors tend to involve the vertebral body

# LANDMARKS

- Oropharynx and soft palate with mouth open
- C3------Hyoid bone
- Level of the larynx in infants-----C2-C3
- Level of the larynx in adults-----C3-C6
- C3-C4: -----Bifurcation of common carotid artery

- Carina-----T3-4 or T4
- Manubrium Sterni-----T3 & T4
- Sternal angle-----T4 & T5
- Body of sternum-----T5to T9 vertebra
- Greater splanchnic nerve------T5-T9 sympathetic ganglia
- Xiphoid process-----T9
- Lesser splanchnic nerve-----T10-T11 sympathetic ganglia
- Least splanchnic nerve-----T12 sympathetic ganglion
- Transpyloric plane-----L1
- Celiac trunk------L1 superior border
- Superior mesenteric artery------L1 inferior border
- Left renal vein------12
- Inferior mesenteric artery-----L3
- Subcostal plane-----L3
- Spleen-obliquely along axis-----10th rib
- Pancreas head------L2 & L3
- Umbilicus(in supine/recumbent position)-disc between L3-L4
- Anterior superior iliac spine-S1/sacral promontory
- Posterior superior iliac spine-S2

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Median Arcuate ligament of respiratory diaphragm- T12 &L1 junction

### Common Bifurcation: TLC-4

- The Common carotid artery bifurcate at------C4

- In the cervical spine and L4, the lateral process is absent

**Back And General Anatomy** 

### Joints Classification

### 1) Joints can classified according to their degree of freedom

- Synarthrosis------Little or no movement
- Amphiarthosis------Slightly moveable joint
- Diathrosis———Freely moveable joint
- Joints are also classified according to the manner in which the adjacent bones are joint. In these two systems, term of classification overlap



There are three types of fibrous joint

- Sutures---joint between the bone of the skull
- Gomphoses-----Teeth in the socket
- Syndesmoses----
  - ✓ Syndesmoses are joints in which bone are connected by ligament only, these are Amphiarthosis
  - ✓ E.g. distal/inferior Tibiofibular joint, middle Radioulnar joint

### **Cartilaginous Joint**

### General characteristic:

- Articulating surface are united by cartilage
- · No joint cavity
- 1) Primary:
  - Also called Synchondrosis
  - No moment, temporary joint (ossify later)
  - Bone united by plate or bar of hyaline cartilage
  - Example:
    - ✓ Joint Between Epiphysis and diaphysis
    - ✓ Ist costochondral joint (between first rib and sternum)

### 2) Secondary:

- Also called as Symphysis
- · Little movement, permanent joint
- Bones are united by Fibrocartilage
- These are called midline joint
- · Example:
  - ✓ The joint between the vertebral bodies (Intervertebral discs),
  - ✓ Symphysis pubis
  - ✓ Symphysis Manti,
  - ✓ Manubriosternal joint

### Chapter 6

**Back And General Anatomy** 

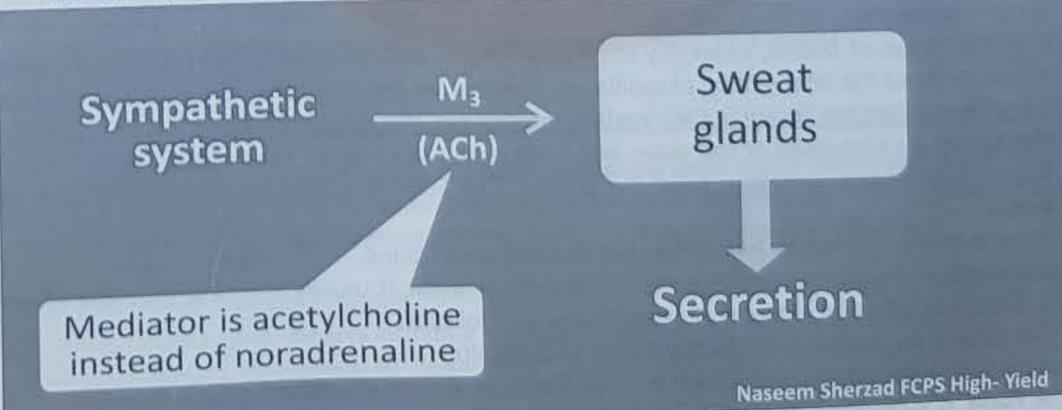
### Synovial Joint

- A synovial joint, also known as Diarthrosis
- Has joint cavity
- Diarthrosis joints are the most flexible type of joint between bones, because the bones are not physically connected and can move more freely in relation to each other.
- Synovial joints are the most common type of joint in the body
- The articular surface of the bone is covered by a thin layer of hyaline cartilage separated by a joint cavity,
- · Synovial joints can be classified according to the arrangement of the articular surface and the types of movements that are possible:
  - Plane (flat), These joints allow for gliding movements, and so the joints are sometimes referred to as gliding joints, acromioclavicular joints, Sternoclavicular joint
  - Hinge joint:----Elbow joint, Knee joint, Ankle joint, interphalangeal joint
  - Pivot-----atlantoaxial joint, proximal Radioulnar joint Bicondylar (two sets of contact points),
  - Condyloid joint: Small amount of rotation is possible e.g. Metacarpophalangeal joint
  - Ellipsoid: Rotation is impossible e.g. wrist joint----important
  - Saddle: Carpometacarpal joint of the thumb-----important
  - Ball and socket---Shoulder joint, Hip joint, Joint between stapes and incus

Innervated by sympathetic nervous system

NASEEM SHERZAD FCPS -1 HIGH-YIELD

- Contain M3, Muscarinic receptors
- Mediator: Acetylcholine instead of nor-adrenaline
- Sweat glands are not present on red margins of lips, nail buds, Glans penis, clitoris
- Sweat glands expand the full thickness of dermis and their extremity may lie in the superficial fascia. They are the most deeply placed structure of all appendages.



### Skin Appendages

- Skin appendages are skin-associated structures that serve a particular function including sensation, contractility, lubrication and heat loss. In humans,
- In burns need of the skin graft is decided on basis of skin appendages
- Some of the more common skin appendages are:
  - Hairs:---- sensation, heat loss, filter for breathing, protection
  - Arrector pili---smooth muscles that pull hairs straight
  - Sebaceous glands-----secrete sebum onto hair follicle, which oils the hair
  - Sweat glands:----can be sweat secreted with strong odor (apocrine) or with a faint odor (eccrine))
  - Nails-----protection

## General Anatomy Important Points

- Hilton's law: sensory nerve supplying the joint also supplies the muscle that causes movement on that joint and the skin overlying the insertion of these muscles
- Nerve to the muscle is mixed nerve, 60% is motor and 40% is sensory
- Hair follicles are invaginations of the epidermis into the dermis.
- Arrector pili are the bands of smooth muscles that connect the undersurface of the hair follicle to the superficial part of the dermis. Dimpling of skin called gooseflesh is due to the pull of the Arrector pili muscle. It causes contraction of the sebaceous gland and its secretion.
- Sebaceous glands lie within the dermis and pour their secretion, the sebum ONTO the shaft of hairs.
- Sebaceous glands are not present in lips, palms, sides of fingers, Glans penis and clitoris, labia minora and internal surfaces of labia majora, soles, sides of feet and sides of toes.
- Flexion and extension takes place in sagittal section
- Adduction and abduction take place in coronal section
- The Dermis is thinner on anterior surfaces of the body as compared to posterior surfaces
- Superficial fascia is devoid of adipose tissue in eyelids, auricles, penis, scrotum and clitoris
- In syringomylia, the pain sensation is lost in joints.
- Tendons invaginate the synovial sheath from a side and are suspended by mesotendons. Mesotendons transmit the blood vessels. In areas where a wide range of movement is there, these mesotendons remain as vinulae.
- In certain areas of bodies, especially the tips of fingers and toes the arteries and vein connect directly without the intervention of capillaries. These areas are called arteriovenous Anastomosis
- Lymphatic vessels are absent in CNS, eyeball, internal ear, the epidermis of skin, cartilage, bone.
- Flat bones are composed of the outer and inner layers of compact bone called the TABLES and middle layer of the cancellous bone the DIPOLE. The Scapula is irregular but is included in flat bones.
- A boil is an infection of the hair follicle and the sebaceous gland.
- Carbuncle is a staphylococcal infection of superficial fascia. It usually occurs at the nape of neck and starts as infection of the hair follicle or group of follicles.
- The Sebaceous cyst most frequently occurs at the scalp.
- Patient of shock exhibits gooseflesh as a result of over activity of sympathetic.
- A Fossa is a pinpoint depression or hollow usually in a bone such as hypophysial fossa, the

### Chapter 6

### **Back And General Anatomy**

#### depression in the sphenoid bone

- A fovea is a small pinpoint pit, usually on the head of the bone. The most well-known example of a fovea is the fovea centralis, a depression in the retina of the eye
- In adult bone marrow formation not occurs in the shaft of the radius
- Lateral process of sacrum fuse to form the median sacral crest
- Mass of hair shaft is mainly due to cortex
- Circumduction: Combination of Flexion, Extension, Adduction and Abduction
- Fowler's position is a standard patient position in which the patient is seated in a semi-sitting position (45-60 degrees) and may have knees either bent or straight. It increase the risk of pressure to scapula, sacrum, coccyx, ischium, back of knee and heels. It also increase risk of air embolism if venous sinus is opened. Fowler position increases the risk of thrombosis as a result of stasis of blood in the leg that why fowler position is dangerous due stasis of blood in leg and which increase the risk of thrombosis

### **Pennate Muscle**

#### 1) Unipennate:

Fibers on one side of tendon e.g. extensor digitorum

#### 2) Bipennate:

- Fibers on both sides of tendon e.g. deltoid
- Tendon branches with muscle e.g. deltoid

### 3) Multipennate:

- Forms angle with tendon
- Donot moves as far as parallel muscle
- Contain more myofibrils than parallel muscle
- Develop more tension than parallel muscle
- Strongest muscle according to its architecture is Multipennate

### Replantation

### General operative sequence of replantation

- 1. Vascular shunt first (for proximal replantation with large muscle mass to minimize warm ischemia time)
- 2. Bone fixation +/- shortening (after irrigation and debridement of soft-tissue and bone)
- extensor tendon repair
- 4. Artery repair (repair second after bone if ischemic time is >3-4 hours)
- Venous anastomoses
- flexor tendon repair
- nerve repair
- 8. In replantation of imputed digits IST bone shortening done which allows skin to be debrided back to where it is free of contusion and direct tension free closure to be achieved. Than in the order of repair usually bone tendon, muscle unites, arteries and finally vein

### 2) Replant monitoring

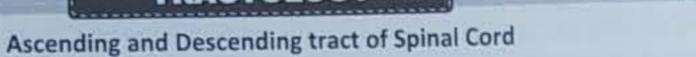
- skin temperature most reliable
  - o concerning changes include a > 2° drop in skin temp in less than one hour or a temperature below 30° celsius
- Pulse oximetry
  - < 94% indicates potential vascular compromise

## CHAPTER

## NEUROANATOMY NEUROPHYSIOLOGY

# & NEUROPATHOLOGY





### General overview

- Ascending tracts
  - ✓ Sensory
- Descending tracts
  - ✓ Motor

### General Arrangement of both tracts

- 1st order neuron
- 2nd order neuron
- 3rd order neuron
- The only difference is the different locations where each order of neuron ends.
- Decussation is the crossover of the tract from one side to the other. Therefore, there are instances where the left side of the body is controlled by the right brain hemisphere. Decussation occurs at different locations for each tract.

### Sensory Ascending System



#### 1) Overview:

- 2<sup>nd</sup> order neuron————Decussates
- 3<sup>rd</sup> order neuron———Thalamus
- Ventral posterolateral nucleus (VPL)------Cortex

### 2) Anterolateral (Spinothalamic) system:

- Pain and temperature fibers have cell bodies in the dorsal root ganglia and enter the spinal cord via A-delta and C or class 3 and 4 dorsal root fibers
- A Primitive system, low velocity and low myelinated system
- . The Spinothalamic tract course through the entire length of the spinal cord
- Anterior/ventral:
  - ✓ AC—Crude pressure and Crude Touch—PT
  - ✓ Ventral Spinothalamic tract end at lumbar region means present at all over the spinal card level

#### Lateral:

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✓ PT—Pain and Temperature

#### Lesion:

✓ Pain and temperature information crosses almost as soon as it enters the spinal cord, any unilateral lesion in the Spinothalamic tract in the spinal cord or brain stem will result in a contralateral loss of pain (anesthesia) and temperature

### 3) Dorsal Column-Medial Lemniscal system: (DCML Pathway)

- Class 2 fiber or A-beta dorsal root fibers
- Modern system, high velocity and highly Myelinated
- Fasciculus cuneatus: Found only at upper thoracic and cervical spinal cord level, is lateral to the fasciculus Gracilis and carries input from the upper extremities and upper trunk.
- Fasciculus Gracilis: found at all spinal cord level, Lower body, situated close to the midline and carries input from the lower extremities and lower trunk----remember this by Gracilis muscle of the leg

#### Function:

- ✓ Two-point tactile Discrimination: the ability to recognize that two blunt points closely applied to the skin are not a single point
- ✓ Stereognosis (recognition of object size, basic shape and texture) and graphesthesia (identification of letters and number written on the skin)
- ✓ Conscious proprioception: Limbs/Joint position and direction of movement
- ✓ Sense of position and vibration
- Sense of fullness of bladder and rectum

#### Lesion of the dorsal column:

- ✓ Result in loss of joint position sensation, vibratory and pressure sensation and 2point discrimination
- ✓ Typically, dorsal column medial lemniscal system are evaluated by testing vibratory sense using a 128 Hz tuning fork
- ✓ Romberg sign is also used to distinguish between lesions of the dorsal column and the midline(vermal) of the cerebellum
- ✓ Positive Romberg sign: swaying toward the side of the lesion, only when the eyes are closed, suggesting that the lesion is in the dorsal column (the dorsal root of spinal nerves)
- Negative Romberg sign: swaying even when the eyes are open, seen in cerebellar ataxia
- Nucleus Gracilis and cuneatus lesion causes--------Astereognosia (ability to perceive the form of a solid object by touch)



### **Descending Tracts**



### Types of descending tracts:

- Lateral corticospinal tract
- Anterior corticospinal tract
- Therefore, the descending tract is also known as the corticospinal tract

## **Corticospinal Tract**



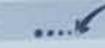
- Corticospinal tracts are particularly concerned with the control of fine voluntary, discrete, <u>skilled</u>
   <u>movements</u> especially those of the distal parts of the limb
- · Origin:
- ✓ 60% of fibers originates from the primary motor area, the Premotor area, and the supplementary motor area of the frontal lobe
  - ✓ Other fibers originates from the primary sensory area, the parietal cortex and the parietal operculum
  - ✓ The main effectors or motor neurons (efferent neurons) for voluntary movement lie within layer V of the primary motor cortex and are a type of giant pyramidal cell called Betz cells.

### Corticospinal tract syndrome:

- It is also known as upper motor neuron syndrome
- · Changes:
  - ✓ Muscles weakness
  - √ Spasticity
  - ✓ Babinski sign and ankle clonus is present or positive
  - ✓ Deep tendon reflex increased or present
  - ✓ Clasp-knife response

Lateral corticospinal tract	Ventral corticospinal tract
80-90% of fibers	<ul> <li>Remaining 10% of fibers</li> </ul>
Descend contralaterally in the lateral     column of the opposite side	<ul> <li>Descend ipsilaterally in the ventral column on the same side</li> </ul>
Along the whole length of the spinal cord	Till the mid-thoracic region only
<ul> <li>Terminate gradually on the laterally situated neurons on the ventral horn directly or more common indirectly through interneuron</li> </ul>	Terminate gradually by crossing various level of the spinal cord to terminate or the medially situated neurons directly of more common indirectly through interneuron
<ul> <li>It is classified as a part of "lateral motor system"</li> </ul>	It is classified as a part of "medial moto system"

### Homunculus arrangement

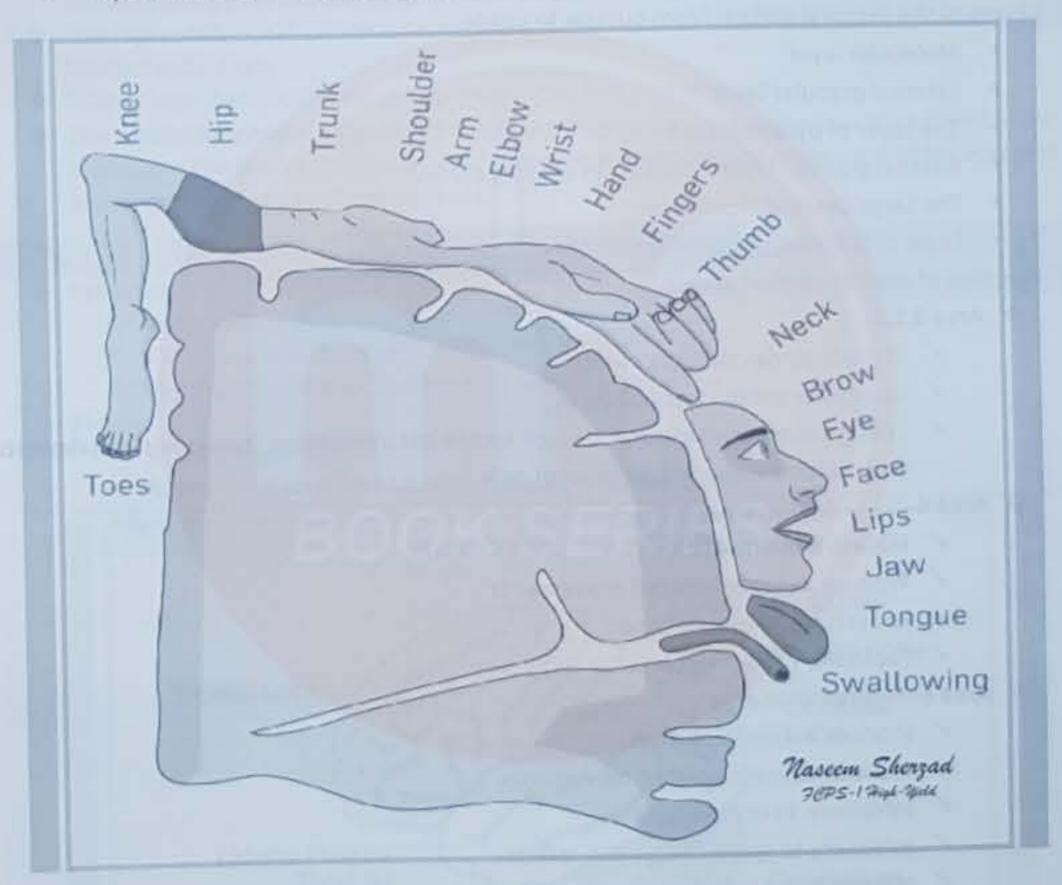


Arranged upside down

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Chapter 7

- . The finer the movement, the more the cortical representation
- Fingers--thumb, face, tongue More
- Trunk, lower limbs Less
- Medial surface: lower limbs
- Superolateral surface: everything else



### Chapter 7

The Cerebrum is the largest part of the brain and consists of the cerebral cortex, which is responsible Cerebral Cortex

for motor, sensory and cognitive functions.

### 1) Cells of the cerebral cortex:

- Pyramidal cell
- Non-pyramidal cell:
  - √ Stellate cell
  - ✓ The Horizontal cell of Cajal
  - ✓ Martinotti cell

# 2) Layers of the cerebral cortex: From outside to inside

- Molecular layer
- External granular layer
- The Layer of pyramidal cell
- Internal granular layer—thickest in sensory cortex
- The Large pyramidal cell layer
- Layer of fusiform or polymorphic cells (multiform layer)

### 3) Function of specific cortical areas:

- ❖ Area 3,1,2:
  - ✓ Primary somatosensory cortex
  - ✓ Located in the postcentral gyrus
  - ✓ Lesion cause contralateral loss of tactile discrimination, two-point discrimination and position sense but no relief of pain

### Area 4-----Motor area

- √ Initiate movements
- ✓ Produce delicate isolated movements
- √ Facilitatory to muscle tone
- ✓ Facilitatory to spinal center and reflexes

### . Area 6----Premotor area

- ✓ Produce automatic action
- ✓ Produce delicate isolated movements
- ✓ Inhibitory to muscle tone
- ✓ Inhibitory to spinal center and reflexes
- ✓ Initiates grasp reflex.

### Area 8----Frontal Eyefield

- ✓ It is a part of the accommodation reflex pathway.
- ✓ Its stimulation results in conjugate deviation of both eye to the opposite side.

### Occipital lobs

- ✓ Area 17——Visuo-sensory area—-receive visual sensation
- ✓ Area 18 & 19---Visuo psychic area---understanding meaning of the seen object

Chapter 7

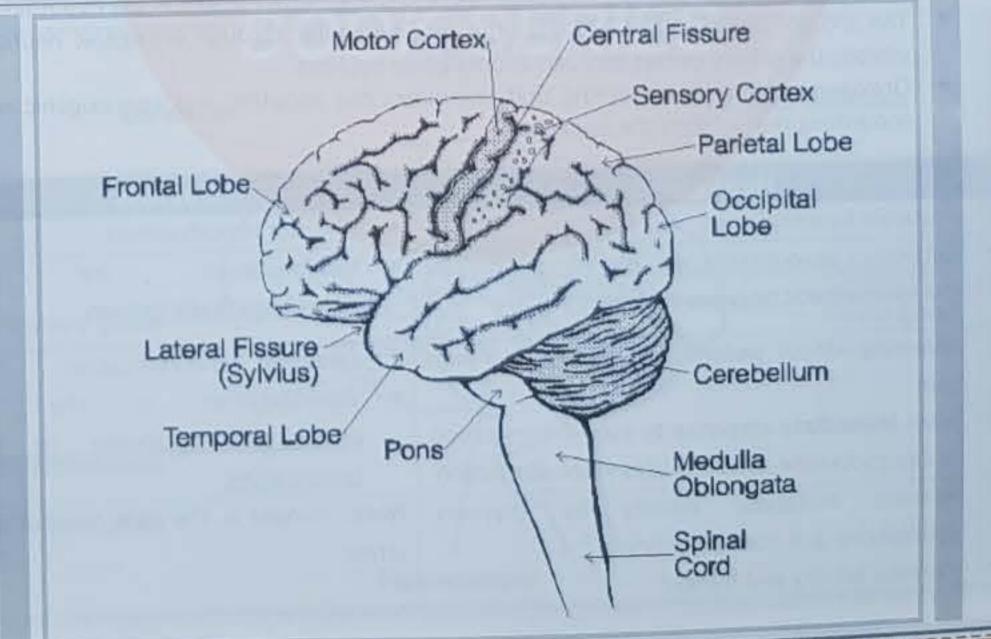
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Neuroanatomy, Neurophysiology & Neuropathology

### Naseem Sherzad High-Yield Points

- Primary auditory cortex present in superior temporal gyrus and bilateral destruction of primary auditory cortex lead to total deafness
- Left insular cortex: For the perception of disgust
- Blood supply of cerebral motor cortex: Anterior and Middle cerebral artery
- In sensory cortex layer IV is thickest
- In motor cortex layer V is thickest
- . The motor cortex is also known as the agranular cortex because of the masking (attenuation) of the granular layers, particularly the inner granular layer. The somatosensory cortex is different from the primary motor cortex in the granular layer
- The representational cerebral hemisphere is the right cerebral hemisphere in most righthanded individuals
- Frontal lobe dysfunction cause depression and loss of motivation
- . The medial longitudinal fasciculus (MLF) is a myelinated composite fiber tract found in the brainstem. The MLF primarily serves to coordinate the conjugate movement of the eyes and associated head and neck movements.

- Extensor:
  - ✓ Antigravity muscle
  - ✓ VIP makes you stand up
  - ✓ Vestibulospinal tract and Pontine Reticulo-spinal tract
- Flexor:
  - ✓ Sit on Rubber Mat
  - ✓ Rubrospinal tract and Medullary Reticulo-spinal tracts



Hypothalamus

- 1) Ventro-Medial hypothalamus:-----Satiety center

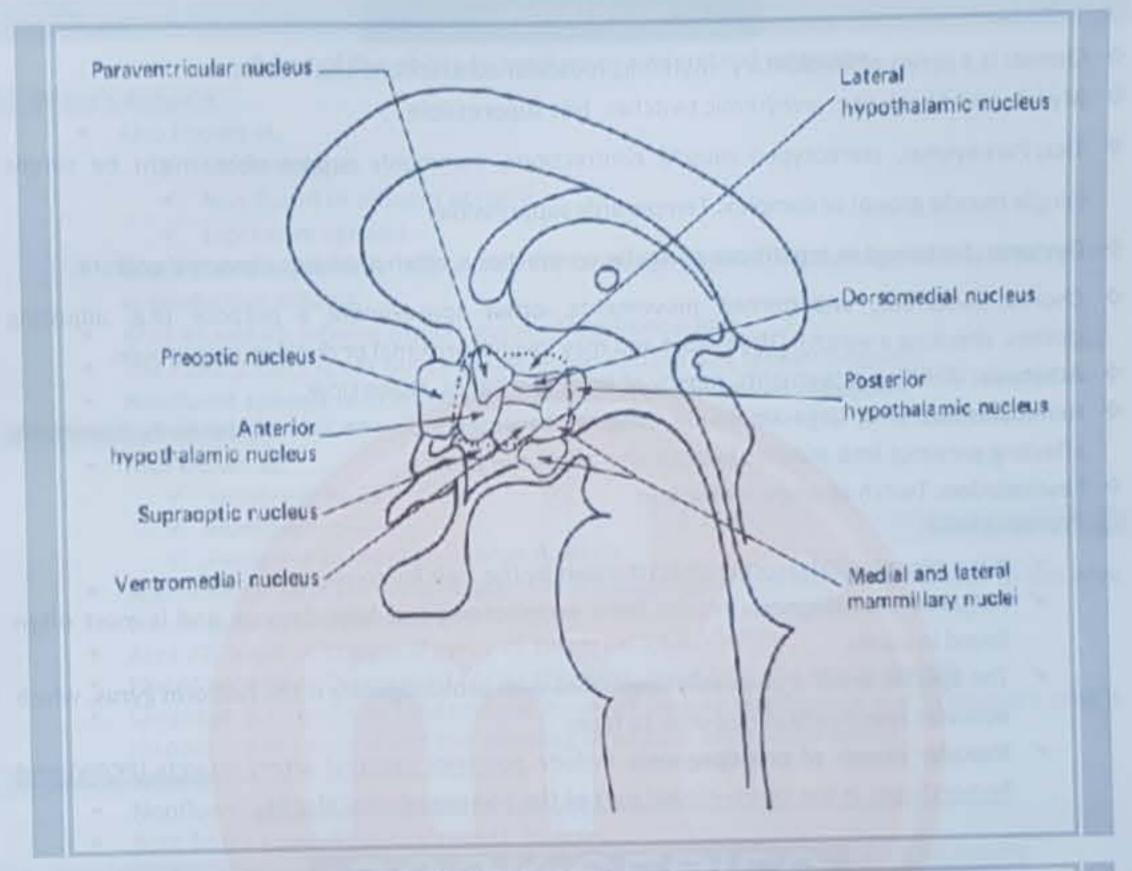
  - ✓ When stimulated, it causes the sensation of fullness and Anorexia Stimulation cause:
    - ✓ Aphagia, weight loss
  - Injury:
    - ✓ Savage behaviorand Hyperphagia
    - ✓ Overeating or excessive eating
    - ✓ Gain weight, Obesity
- 2) Lateral hypothalamus: Feeding or Hunger center
  - Leptin decreasing appetite———Cause Loss of appetite
  - Ghrelin increasing appetite——Cause Gain of appetite
  - Stimulation cause:
    - ✓ Increased feeding
  - · Injury:
    - ✓ Decreased feeding
    - ✓ Loss of weight and Starvation
- Finally, there's the arcuate nucleus which is like a switchboard that receives various signals 3) Arcuate nucleus: from the gastrointestinal tract. This nucleus sends neuron fibers to regulate the feeding
  - Alright, let's say you forgot to buy lunch, and it's the late afternoon. Two things happen to trigger your hunger. First, mechanoreceptors in your stomach detect that your stomach is empty, so they fire slowly through the vagus nerve to a cluster of neurons in the medulla called the solitary nucleus.
  - The solitary nucleus then sends nerve fibers to the arcuate nucleus in the hypothalamus,
  - The arcuate nucleus then activates the feeding center through orexigenic neurons, and inhibits the satiety center through anorexigenic neurons.
  - Orexigenic refers to something that stimulates the appetite, and anorexigenic refers to something that inhibits the appetite

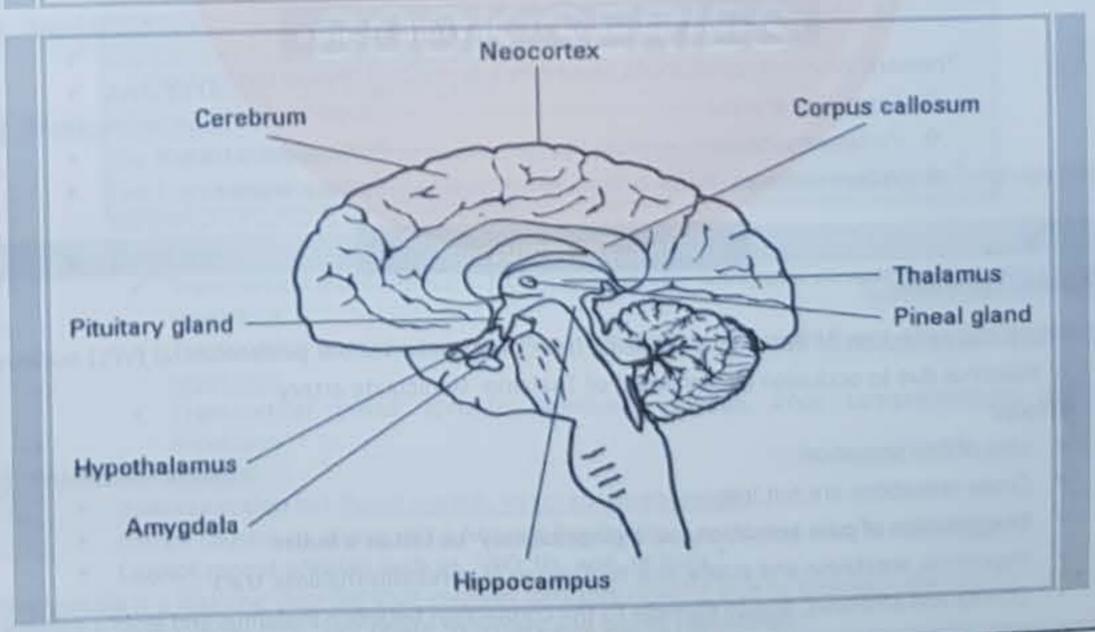
-	Heat gain	Heat loss
	Posterior hypothalamus	Anterior hypothalamus
	Cutaneous vasoconstriction and Piloerection the sympathetic nervous system	vasodilatation by the parasympathetic system
	ShiveringMost potent mechanism for he gain  Most immediate response to coldstimulat of catecholamine, which causes vasoconstriction	vasodilatation is the physiological response to high temperature
	Increase metabolic activity by thyro epinephrine and nor-epinephrine Increase activity and hunger	xin, Note: Hunger is the best psychological stress

Chapter 7

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Neuroanatomy, Neurophysiology & Neuropathology





### **Some Definition**

- . Clonus: is a series of involuntary, rhythmic, muscular contractions and relaxations
- Myoclonus: Shock-like, arrhythmic twitches. Not suppressible.
- \* Tics: Paroxysmal, stereotyped muscle contractions, commonly suppressible, might be simple (single muscle group) or complex. Temporarily suppressible.
- ❖ Dystonia: Sustained or repetitious muscular contractions, often produces abnormal posture.
- . Chorea: Dance-like, unpatterned movements, often approximate a purpose (e.g. adjusting clothes, checking a watch). Often rapid and may involve proximal or distal muscle groups.
- \* Athetosis: Writhing movements, mostly of arms and hands. Often slow.
- . Hemiballismus: wild, large-amplitude, flinging movements on one side of the body, commonly affecting proximal limb muscles but can also affect the trunk.
- \* Fasciculation: Twitch of single motor unit

### Prosopagnosia:

- ✓ it is a neurological disorder characterized by the inability to recognize faces
- ✓ Acquired prosopagnosia results from occipitotemporal lobe damage and is most often found in adults.
- ✓ The specific brain area usually associated with prosopagnosia is the fusiform gyrus, which activates specifically in response to faces.
- Vascular causes of prosopagnosia include posterior cerebral artery infarcts (PCAIs) and hemorrhages in the infero-medial part of the temporo-occipital area.

### **Naseem Sherzad High-Yield Points**

Tremors: Rhythmic oscillations caused by intermittent muscle contractions

- -----Intention tremor Cerebellar disease---
- Parkinson disease-----Resting/static tremor
- Wilson disease-------Postural tremor

### Thalamus

### Thalamic syndrome:

- This is the collection of symptoms resulting from damage to ventral posterolateral (VPL) nucleus of thalamus due to occlusion (thrombosis) of Thalamo- Geniculate artery
- Effects:
  - ✓ Loss of fine sensation
  - ✓ Crude sensations are not lost
  - Exaggeration of pain sensation, so, a pinprick may be felt as a bullet
  - ✓ Hypotonia, weakness and ataxia, due to damage of cerebello-thalamic tract
  - Chorea and athetosis, due to damage to the connection between thalamus and globus pallidus

### Chapter 7

### Neuroanatomy, Neurophysiology & Neuropathology

### **Aphasia**

### A loss of the ability to produce or understand language

### 1) Broca's Aphasia:

Also known as,

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- ✓ Motor aphasia
- ✓ Non-fluent or affluent aphasia
- ✓ Expressive aphasia
- Broca's area is primarily responsible for language production; damage to this area results in productive aphasia.
- Area 44 and 45, inferior frontal gyrus of the frontal lobe
- The Patient can't speak but can understand written and spoken language
- Nonfluent aphasia with intact comprehension and impaired repetition

#### 2) Wernicke's aphasia

- Also known as;
  - ✓ Sensory aphasia
  - ✓ Fluent aphasia,
  - ✓ Receptive or rapid non-sense Aphasia
- Wernicke's area is primarily responsible for language comprehension; damage to this area results in receptive aphasia.
- Area 22, superior temporal gyrus of temporal lobe
- Fluent aphasia with impaired comprehension, repetition and empty speech
- Language is one of the fundamental bases of human intelligence and Wernicke's area is responsible to comprehend the meaning of written and spoken words

### 3) Global aphasia:

- Nonfluent aphasia with impaired comprehension
- Both Broca's and Wernicke's areas affected

### 4) Anomic aphasia:

- ✓ The person has word-finding difficulty
- ✓ Area 39 Lesion in the angular gyrus

### 5) Transcortical aphasia:

- The linguistic opposite of conduction aphasia is Transcortical aphasia
- The Transcortical aphasia is characterized by the intact repetition of spoken language but disruption of other language function
- Three types:
  - ✓ Transcortical motor aphasia: Nonfluent aphasia with good comprehension and intact repetition
  - ✓ Transcortical sensory aphasia: Poor comprehension with fluent speech and intact repetition
  - Transcortical mixed aphasia: Nonfluent speech, Poor comprehension, intact repetition
- 6) Conduction aphasia:
  - Poor repetition but fluent speech, intact comprehension
  - Can be caused by damaged to Arcuate fasciculus
  - Cannot repeat phrases such as, "NO, ifs, and, or buts."
- 7) Dyslexia is a learning disorder that involves difficulty reading due to problems identifying speech sounds and learning how they relate to letters and words (decoding).

### Sleep Physiology

- Non-rapid eye movement (NON-REM Sleep): 75%
  - Regulate by the brain stem
  - Bedwetting
  - Sleepwalking
  - Night terror, usually occurs in stage 3 or 4 of non REM sleep, it is characterized by brief,
     wild behavior
  - Raphe nucleus is situated in lower pone and medulla. Activation of this nucleus results in non-REM sleep. It is due to the release of serotonin by the nerve fiber arising from this nucleus. Serotonin induces non-REM sleep
- Rapid eye movement (REM Sleep): 20-25% of total sleep
  - Regulate by high brain center, Pons
  - Pupillary constriction
  - Penile erection
  - Nightmares, a nightmare is simply a "bad sleep" which the individual typically remember after awakening, its occurs in both adults and children
  - Role of locus coeruleus of pons: activation of this center produces REM sleep. Nonepinephrine released by the nerve fibers arising from locus coeruleus induces REM sleep
- Waves:
  - Beta wave: ———REM, open eye —— BRO
  - Alpha wave:——close eye
- Stage of sleep
  - Stage 1:----LighT sleep-----TheTa wave
  - Stage 2: K2

    K2 complex spindles
  - Stage 3+4:—Deep sleep————Delta wave
- No change occurs in ECG during sleep
- Normal sleep requirement:
  - Newborn------- 16-20 hr/day

  - Adults ---- 7-9 hr/day
  - Old-----5 hr/day

### Chapter 7

## Neuroanatomy, Neurophysiology & Neuropathology

### **Limbic System**

- Responsible for feeding, fighting, feeling, flight and sex
- Circuit: Hippocampus-----------fornix-------------mammillary body----------------hippocampus(role in memory and spatial cognition, Alzheimer result in degeneration of hippocampus)
- Activate at the onset of puberty

### Function

- ✓ Feeding, chewing and licking by amygdaloid
- ✓ Emotion, e.g. fear, sweating, pupillary dilation, pleasant or unpleasant by amygdaloid
- ✓ Rage and placidity
- ✓ Autonomic function, heart rate, BP, respiratory rate etc.
- ✓ Maternal behavior, prolactin, lactation etc.
- ✓ Motivation e.g. reward and punishment
- ✓ Learning and emotional behavior

### Kluver Bucy syndrome:

- ✓ Bilateral lesions of amygdale
- ✓ Characterized by:
  - Inappropriate sexual behaviors and mouthing of objects
  - Visual agnosia
  - o Hypermetamorphosis
  - o Hyperphagia
  - Hypersexuality

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#### **Deviation Differences**

## Deviation to the same side of lesion:

- 12 nerve palsy: tongue Deviate toward the side of the lesion on the protrusion ("lick your wound")
- · Vocal cord
- Cerebellum lesion
- 5<sup>th</sup> nerve palsy: Jaw deviate toward the side of the lesion

### Deviation away from the side of lesion:

- 10 CN nerve lesion: Uvula deviate away from the side of lesion, weak side collapse and uvula points away
- Internal capsule:
  - ✓ Uncrossed lesion
  - ✓ Right hemiplegia with right facial nerve palsy lesion will be in the internal capsule.
- Facial nerve:
  - UMN Lesion-----Contralateral lower face paralysis & Sparing Forehead
  - LMN Lesion ------Ipsilateral upper and lower face including forehead
  - Bilateral facial palsy----Lyme disease

ventricle.

Neuroanatomy, Neurophysiology & Neuropathology

## Ventricular System of Brain

There are 4 interconnected ventricles in the brain: 2 lateral ventricles, a third ventricle and a 4<sup>th</sup>

### Lateral Ventricle

- The 2 lateral ventricles, 1 in every cerebral hemisphere, create the largest component of the ventricular system
- The lateral ventricles are bilateral C-shaped structures that extend through all four lobes of the brain
- Lateral ventricles are separated by the septum pellucidum
- Each lateral ventricle communicates with the third ventricle via Foramen of Monro
- The lateral ventricle has a body or central part and three extensions, namely the anterior, posterior and inferior horns.

#### Third Ventricle

· Present in the midbrain

- The 3rd ventricle is the cavity of the diencephalon
- The Third ventricle is found in the midline within the diencephalon and communicates with the 4<sup>th</sup> ventricle via Cerebral aqueduct, which passes through the midbrain
- The bigger upper part of the lateral wall is composed by the medial surface of the anterior twothird of the thalamus.
- The smaller lower part of the lateral wall is composed by the hypothalamus and it's constant with the ventricular floor.

#### Fourth Ventricle

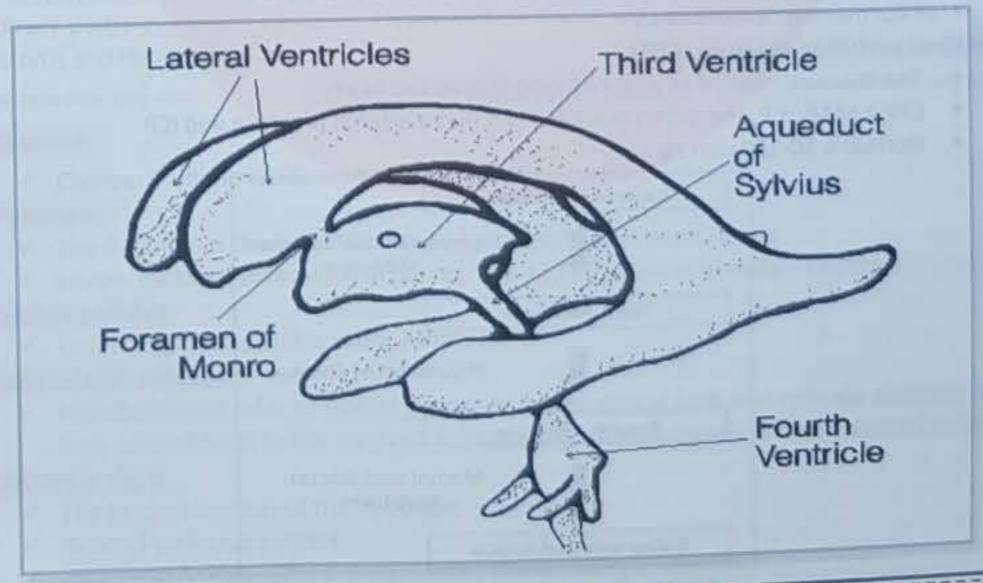
- The 4th ventricle is a tent-like cavity of the hindbrain lined with Ependyma and filled up with cerebrospinal fluid (CSF), it's situated in the posterior cranial fossa in front of the cerebellum and behind the pons and the upper part of the medulla oblongata.
- It's continuous inferiorly with the central canal of the medulla oblongata and superiorly with the cerebral aqueduct of the <u>midbrain</u>.
- The Floor of 4<sup>th</sup> ventricle:
  - ✓ The floor of the 4th ventricle is composed by the posterior surface of the pons and the upper part of the medulla. Its rhomboid in shape (diamond-shaped) and as a result of its shape, the floor of the 4th ventricle is usually referred to as rhomboid fossa.
  - ✓ The whole floor is split into left and right symmetrical halves by a median sulcus, which
    stretches from the aperture of the aqueduct of the midbrain above to the
    commencement of the central canal below.
  - At its broadest part, the floor is crossed transversely by glistening white fibers, the stria medullaris. These fibers are originated from arcuate nuclei, which come from the median sulcus and run transversely across the floor to goes into the inferior cerebellar peduncle.
  - ✓ On either side of the median sulcus, there's a <u>longitudinal elevation referred to as</u> medial eminence.

Chapter 7 Neuroanatomy, Neurophysiology & Neuropathology

- ✓ The medial eminence is bounded laterally by sulcus limitans.
- ✓ At the lateral angle of the floor, the region lateral to sulcus limitans <u>overlies the</u> <u>vestibular nuclei and for this reason, it is referred as the vestibular area.</u>
- ✓ The lowermost part of sulcus limitans presents a small depression referred to as inferior fovea.
- ✓ On either side, the medial eminence presents an oval swelling in the pontine part of the floor in the level of the superior fovea, the facial colliculus. The swelling is generated by the fibers from the motor nucleus of facial nerve hooking around the Abducent nucleus (internal genu of the facial nerve).
- From inferior fovea, the sulcus limitans descends obliquely toward the median sulcus. This sulcus divides the medial eminence in the medullary part of the floor into 2 triangles: the hypoglossal triangle above and the vagal triangle below.
- Foramen of Luschka------Foramen Luschka is Lateral aperture: it allows cerebrospinal fluid to flow out of the fourth ventricle, into the subarachnoid space at the cerebellopontine angle.
- Foramen of Magendie—foramen Magendie is Medial aperture: it links the fourth ventricle and the cisterna magna

#### Cerebral Aqueduct

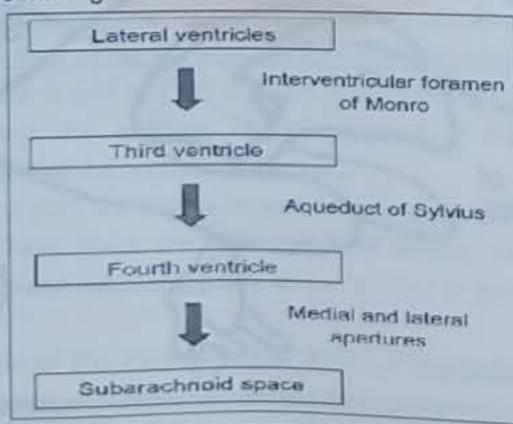
- Connect 3<sup>rd</sup> ventricle with 4<sup>th</sup>ventricle
- . It forms the cavity of midbrain
- Lined by Ependyma and surrounded by gray matter
- It is 1.8 cm
- Ascending reticular formation is present in the floor of the duct
- The most common cause of congenital hydrocephalous is cerebral aqueduct stenosis



## Cerebrospinal Fluid (CSF)



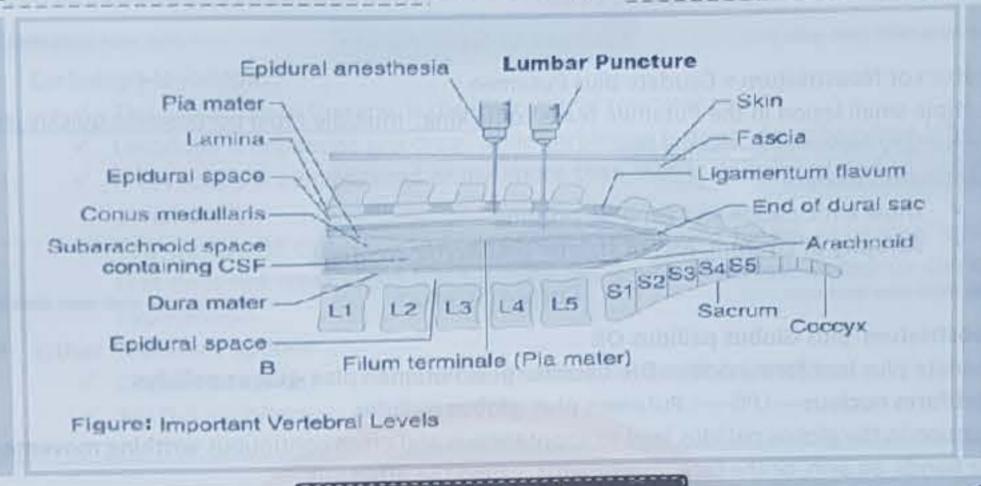
- Actively secreted by Ependymal cell of choroid plexus
- Absorb by arachnoid villi
- Ciliary movements of Ependymal cells Keep CSF in circulation
- CSF pressure can increase by blocking of IJV
- ❖ Volumetric distribution of CSF: Cranial subarachnoid space: 100 ml CSF, Spinal subarachnoid space: 25ml, lateral ventricular horns: 25-30ml, third ventricle: 2-3ml, 4th ventricle: 2-3 ml
- Function:
  - Act as a shock absorber
  - Act as cushions between the soft and delicate brain and rigid cranium
  - Act as a fluid buffer
  - Remove metabolites from the brain
  - Server as a medium for nutritional exchange in CNS
- Composition:
  - ---50-90 mg/dl, decrease glucose than plasma Glucose----
  - ---20-40mg/dl Protein----
  - Normal CSF pressure-10-20 mm Hg or 80-180 mm H<sub>2</sub>0, increased by blockage of the internal jugular vein
  - Osmolarity----<1040
  - pH-----decrease pH of CSF----CSF 7.33 while that of plasma is 7.4
  - Present at one time-----125-150ml, CSF is replaced about four time a day
  - Produce 400-500ml, average 450ml per day at the rate of 25ml/hr
  - Present in the ventricular system---Only 25 ml
  - Having a high chloride level
  - CSF color in TB----straw color
- Lumbar puncture:
  - The Commonest site for LP is-----L4-L5--best site is above L4
  - LP for meningitis—below L3
- Cerebral perfusion pressure (CPP):
  - The Pressure needed to ensure blood flow to the brain
  - CPP = MAP-ICP, the difference between mean arterial pressure and ICP
  - Normal is 50-150 mm Hg



Chapter 7

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## Neuroanatomy, Neurophysiology & Neuropathology



### **Basal Ganglia**

- These are masses of gray matter situated deep within the white matter of cerebral hemisphere
- High O2 consumption and high Content of copper
- They are Separated from thalamus by the posterior limb of the internal capsule
- . Amygdale is part of the limbic system and is attached to the tail of caudate
- The Final neurotransmitter in basal ganglia outflow pathway is GABA

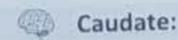
### The Function of basal ganglia

- Starting and stopping voluntary motor function and inhibiting unwanted movement
- It initiates and provides gross control over skeletal muscle movement

### Pathway

- . Direct pathway: lesion cause--------Hypo-kinetic motor disturbance ---like Parkinson disease
- . Indirect pathway—lesion cause-----Hyper-kinetic motor disturbance —like Huntington disease, dystonia and Hemiballismus

#### Nucleus



✓ Chorea: Multiple rapid, random movements

### Putamen:

- √ The Putamen is the Commonest site for hypertensive hemorrhage
- ✓ Lesion: flicking movements in hands, face and other parts of body—Chorea

### Globus pallidus

✓ Defect in globus pallidus cause Athetosis

### Subthalamic nucleus

- ✓ Hemiballismus refer to violent projectile movements of limb and typically observed in upper limb contralateral to the involved Subthalamic nucleus, mostly in the hypertensive patient
- Substantia nigra:
  - ✓ The Largest nucleus of the midbrain
  - ✓ Related with crus cerebri
  - √ Parkinson disease----loss of pigmented Dopaminergic neurons

Neuroanatomy, Neurophysiology & Neuropathology

### Stratum or Neostriatum

- Stratum or Neostriatum = Caudate plus Putamen
- Multiple small lesion in the Putamen leads to flicking, multiple rapid purposeless quickly jerky involuntary movement-dance like
- Huntington disease
  - ✓ show anticipation and genome printing
  - ✓ Atrophy of stratum, loss of <u>striatal GABAergic Neurons</u>

### Corpus Stratum

- \* Neostriatum plus Globus pallidus OR
- Caudate plus lentiform nucleus OR Caudate plus Putamen plus globus pallidus
- Lentiform nucleus—-LPG---: Putamen plus globus pallidus
- \* A Lesion in the globus pallidus lead to spontaneous and often continuous writhing movements in the hands, an arm, or the face, movements called the athetosis

#### **Parallel Circuit**

- \* Skeletomotor loop:-----Control of skeletal muscle
- -Control of extraocular muscle Oculomotor loop: ---
- -Role in cognition Association loop:——
- . Limbic loop: ------Maturation/ emotion

### Blood supply of Basal Ganglia

- . The arterial supply to the basal ganglia comes mainly from middle cerebral artery
- . The main artery is named lenticulostriate artery and, as the name implies, provides most of the circulation to the striatum and the lenticular nucleus

### Diseases of Basal Ganglia

Hyper-kinetic disease:

- · Chorea: Multiple, rapid, random movements
- Athetosis: Athetosis refers to a slow, writhing movement that are noticeable in the fingers and hands but may involve any muscle group
- Wilson disease
- Hemiballismus
- Hypo-kinetic disease
  - Parkinsonism

#### **Parkinson Disease**

- Pathophysiology:
  - Loss of pigmented Dopaminergic neurons from substantia nigra resulting in the deficiency of dopamine
  - Lewy body—intracytoplasmic Esoinophillic inclusion contain alpha-synuclein
- Clinical features
  - · Pathognomonic feature, Pill-rolling (resting) tremor
  - Bradykinesia----slowness of movement
  - Cogwheel rigidity----mostly in upper limb
  - Plastic (lead-pipe) rigidity----mostly in lower limb
  - Shuffling gate, Stooped posture, Masked face, Depression And Dementia

### Chapter 7

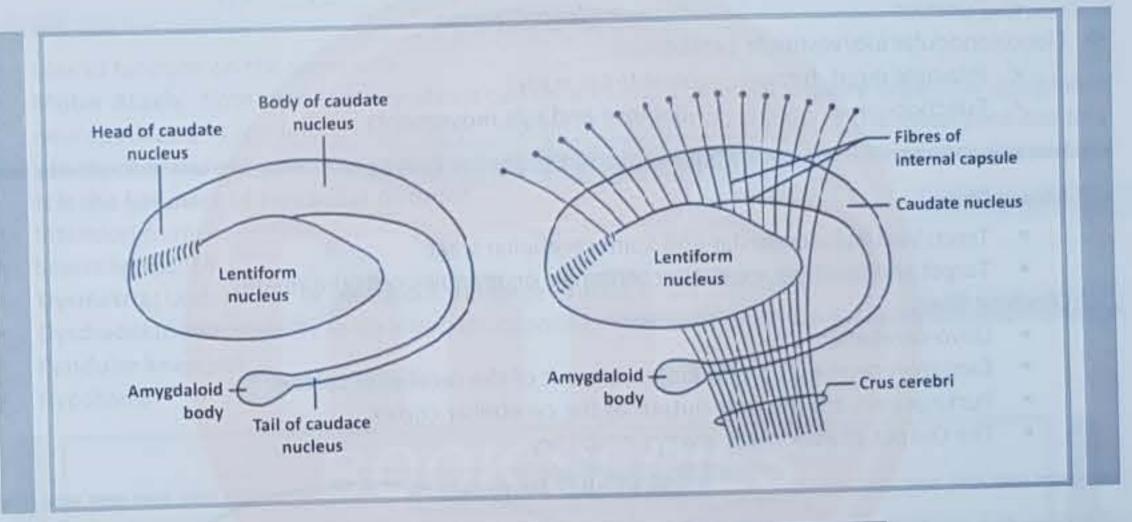
### Treatment: Carbidopa-levodopa:

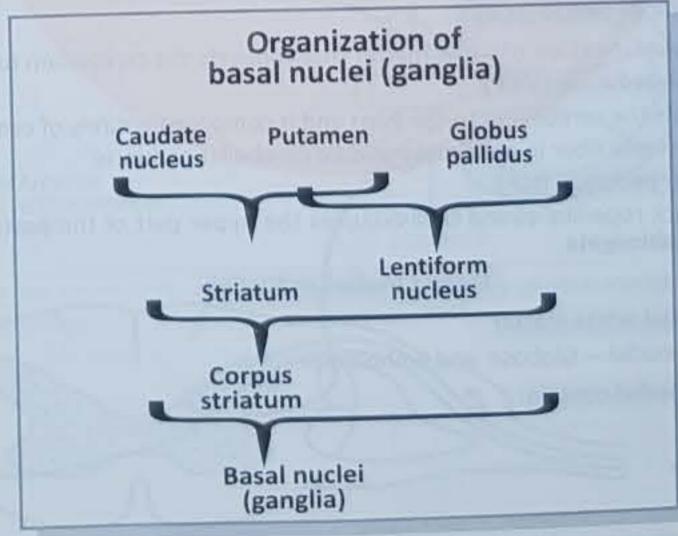
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- ✓ This combination therapy is the mainstay of treatment
- Levodopa is dopamine pro-drug, while carbidopa is dopa- decarboxylase inhibitor
- ✓ If Levodopa is administered orally, more than 90% is decarboxylated to dopamine peripherally
- ✓ This peripheral conversion of Levodopa is minimized by decarboxylase inhibitor. that does not cross blood-brain barrier along with Levodopa. Levodopa can cause hypotension

### Other treatment options:

- Dopamine agonist------Ropinirole, Pramieixole, Bromocriptine
- ✓ MAO-B inhibitors-----Selegiline





### Cerebellum

The cerebellar cortex consist of multiple parallels fold of that are referred as Folia Consist of:

Midline vermis

NAME AND ADDRESS OF THE OWNER, WHEN PERSON NAMED IN

2 lateral cerebellar hemisphere

### Regions And Function of Cerebellum

- · Vermis and intermediate zone/Spino-cerebellum
  - ✓ Principle input from——Spinal cord
  - ✓ Function: ----Ongoing Motor execution
- · Lateral hemisphere/Ponto-cerebellum
  - ✓ Principle input from——Cerebral cortex and inferior olivary nucleus
  - ✓ Function————Planning/coordination
- · Flocculonodular lob/vestibule-cerebellum
  - ✓ Principle input from——Vestibular nuclei
  - ✓ Function———Balance and eye movements

### Major input to Cerebellar Cortex

- Mossy fiber:
  - Tract: Vestibulocerebellar and Spinocerebellar tract
  - Target and function: excitatory terminals on granules cell (glutamate)
- Climbing fiber:
  - Olivo-cerebellar

- Excitatory terminals on Purkinje cells out of the cerebellar cortex
- Purkinje cells are the only output of the cerebellar cortex
- The Output of Purkinje Is always inhibitory

#### Cerebellar Peduncle

- Superior cerebellar peduncle (SCP):
  - It is a paired structure of white matter that connects the cerebellum to the midbrain
- Middle cerebellar peduncle (MCP):
  - It connects the cerebellum to the Pons and is composed entirely of centripetal fibers.
  - . The Transverse fiber in pons make middle cerebellar peduncle
- Inferior cerebellar peduncle (ICP):
  - It is a thick rope-like strand that occupies the upper part of the posterior district of the Medulla oblongata.

### Deep Cerebellar Nuclei

- Lies deep in internal white matter
  - Interposed nuclei— Globose and Emboliform
- From lateral to medial contain:
  - Dentate
  - Emboliform
  - Globose
  - Fastigial nucleus-----Most Medial

Chapter 7

Neuroanatomy, Neurophysiology & Neuropathology

### The Layers of Cerebellar Cortex

My Personal Garden (from outer to inner side)

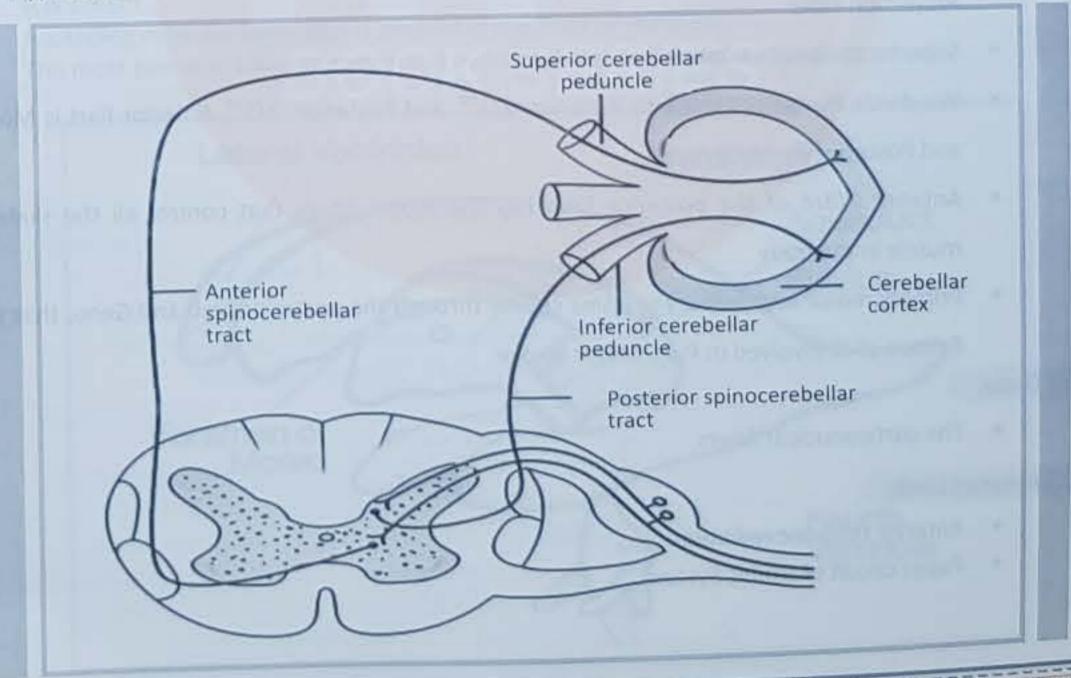
Molecular layer:

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- It is the outer layer and made of Stellate cell and basket cell
- Purkinje layer
  - It is the middle layer and most important layer of the cerebellum
  - The output is always inhibitory
- Granular layer
  - It is the innermost layer and contains 3G----Golgi cell, Granule cell and Glomeruli cell
  - The granule cell is the only excitatory neuron within the cerebellar cortex. All other neurons of the cerebellar cortex are inhibitory

#### Clinical Disorder

- Loss of function on the same side
- Motor Ataxia. Note that Sensory ataxia can be a manifestation of sensory large fiber peripheral neuropathies and conditions causing dysfunction of the dorsal columns of the spinal cord due to a variety of disorders: infectious, autoimmune, metabolic, toxic, vascular and hereditary diseases.
   It is the hallmark of cerebellar disorder.
- Intention tremor
- Scanning speech
- Dysmetria: Undershoot or overshoot the target during finger nose test
- Dysdiadokinesia: inability to do alternate opposite movement rapidly. e.g. supination and Pronation
- Pendular knee jerk
- Hypotonia



Neuroanatomy, Neurophysiology & Neuropathology

INTERNAL CAPSULE

Internal Capsule is nothing but just a Bunch of White Matter fiber

#### Relations

- Medial Side
  - ✓ The tailed nucleus called Caudate Nucleus and Thalamus
- Lateral Side
  - ✓ A Lens Shaped Nucleus called the Lentiform nucleus.
  - Lentiform = Putamen + Globus Pallidus --- LPG

### Composition

- It is composed of ascending and descending nerve
- Fibers that connect the cerebral cortex to the brainstem and spinal cord

#### Components

### Posterior Limb:

- Corticospinal Tracts -Anterior 2/3rd of Posterior Limb
- Extrapyramidal tract
- Optic radiation--Most Posterior in the Posterior Limb, these are **Projection Fiber**
- Superior thalamic radiation
- We divide Posterior Limb into Anterior 2/3<sup>rd</sup> and Posterior 1/3<sup>rd</sup>, Anterior Part is Motor and Posterior Part is Sensory
- Anterior 2/3rd of the posterior limb has the motor fibers that control all the skeletal muscle in the body
- Primary motor and sensory systems course through the posterior limb and Genu, that the Reason of IC Involved in Pure Motor Stroke

### Genu:

The corticonuclear fibers

### Anterior Limb:

- Anterior thalamic radiation
- Papez circuit of Limbic System

✓ The medial eminence is bounded laterally by sulcus limitans.

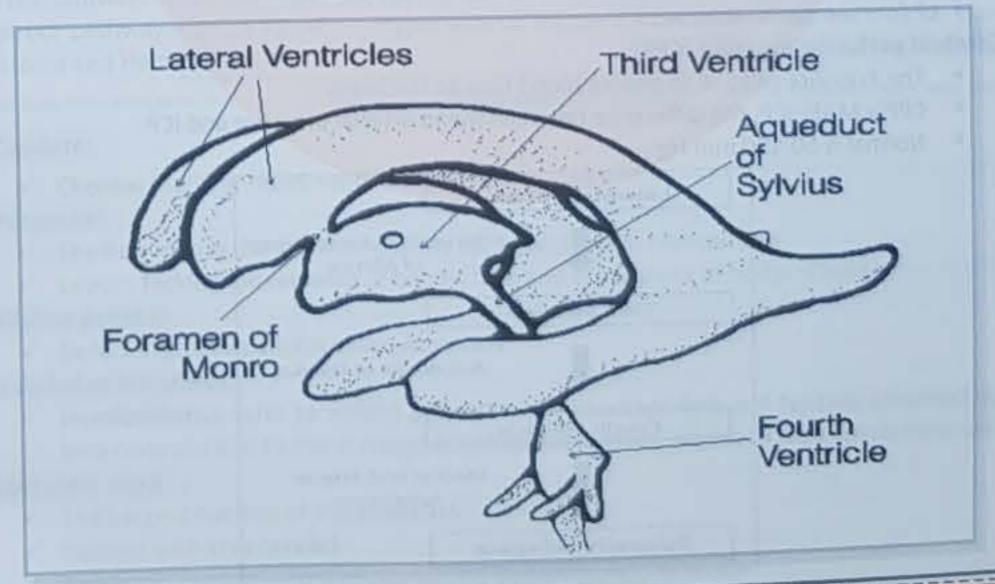
- ✓ At the lateral angle of the floor, the region lateral to sulcus limitans overlies the vestibular nuclei and for this reason, it is referred as the vestibular area.
- ✓ The lowermost part of sulcus limitans presents a small depression referred to as inferior. fovea.
- ✓ On either side, the medial eminence presents an oval swelling in the pontine part of the floor in the level of the superior fovea, the facial colliculus. The swelling is generated by the fibers from the motor nucleus of facial nerve hooking around the Abducent nucleus (internal genu of the facial nerve).
- ✓ From inferior fovea, the sulcus limitans descends obliquely toward the median sulcus. This sulcus divides the medial eminence in the medullary part of the floor into 2 triangles: the hypoglossal triangle above and the vagal triangle below.
- Foramen of Luschka-----Foramen Luschka is Lateral aperture: it allows cerebrospinal fluid to flow out of the fourth ventricle, into the subarachnoid space at the cerebellopontine angle.
- Foramen of Magendie-foramen Magendie is Medial aperture: it links the fourth ventricle and the cisterna magna

### Cerebral Aqueduct

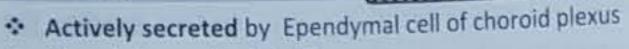
- Connect 3<sup>rd</sup> ventricle with 4<sup>th</sup>ventricle
- It forms the cavity of midbrain
- Lined by Ependyma and surrounded by gray matter
- It is 1.8 cm

Chapter 7

- Ascending reticular formation is present in the floor of the duct
- The most common cause of congenital hydrocephalous is cerebral aqueduct stenosis



# Cerebrospinal Fluid (CSF)



Absorb by arachnoid villi

8 5 a a

- Ciliary movements of Ependymal cells Keep CSF in circulation
- CSF pressure can increase by blocking of IJV
- \* Volumetric distribution of CSF: Cranial subarachnoid space: 100 ml CSF, Spinal subarachnoid space: 25ml, lateral ventricular horns: 25-30ml, third ventricle: 2-3ml, 4th ventricle: 2-3 ml

### Function:

- Act as a shock absorber
- Act as cushions between the soft and delicate brain and rigid cranium
- Act as a fluid buffer
- Remove metabolites from the brain
- Server as a medium for nutritional exchange in CNS

### Composition:

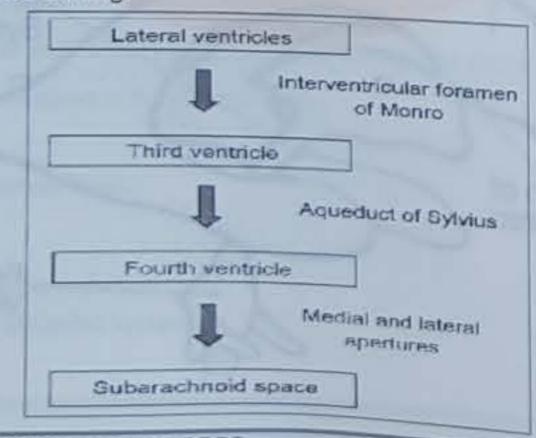
- Glucose---------50-90 mg/dl, decrease glucose than plasma
- Protein-20-40mg/dl
- Normal CSF pressure-----10-20 mm Hg or 80-180 mm H<sub>2</sub>0, increased by blockage of the internal jugular vein
- Osmolarity----<1040
- pH----decrease pH of CSF----CSF 7.33 while that of plasma is 7.4
- Present at one time-----125-150ml, CSF is replaced about four time a day
- Produce 400-500ml, average 450ml per day at the rate of 25ml/hr
- Present in the ventricular system-Only 25 ml
- Having a high chloride level
- CSF color in TB-----straw color

### Lumbar puncture:

- The Commonest site for LP is——L4-L5—best site is above L4
- LP for meningitis---below L3

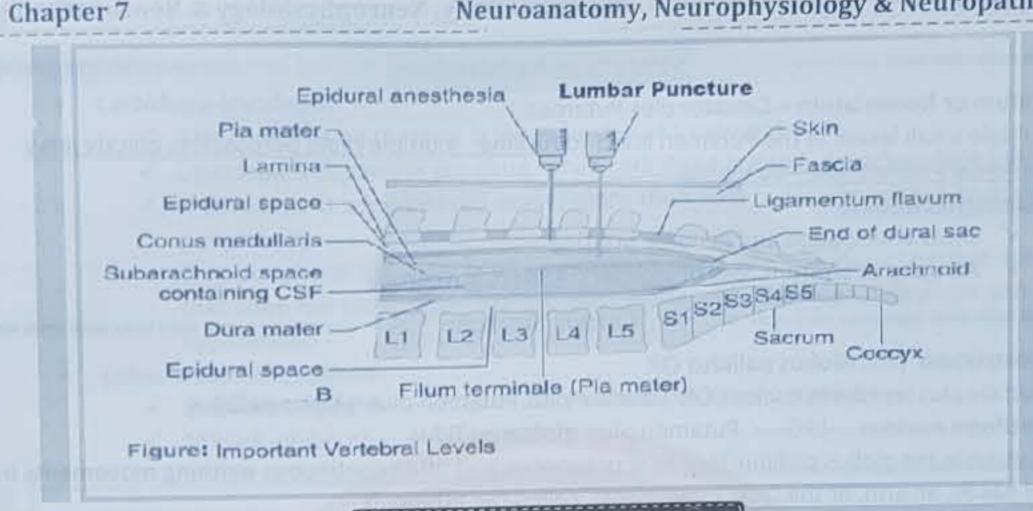
### Cerebral perfusion pressure (CPP):

- The Pressure needed to ensure blood flow to the brain
- CPP = MAP- ICP, the difference between mean arterial pressure and ICP
- Normal is 50-150 mm Hg



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### Neuroanatomy, Neurophysiology & Neuropathology



### **Basal Ganglia**

- \* These are masses of gray matter situated deep within the white matter of cerebral hemisphere
- High O2 consumption and high Content of copper

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- \* They are Separated from thalamus by the posterior limb of the internal capsule
- \* Amygdale is part of the limbic system and is attached to the tail of caudate
- The Final neurotransmitter in basal ganglia outflow pathway is GABA

### The Function of basal ganglia

- Starting and stopping voluntary motor function and inhibiting unwanted movement
- It initiates and provides gross control over skeletal muscle movement

#### Pathway

- \* Direct pathway: lesion cause--------Hypo-kinetic motor disturbance ---like Parkinson disease
- \* Indirect pathway-lesion cause-----Hyper-kinetic motor disturbance -like Huntington disease, dystonia and Hemiballismus

#### Nucleus

### Caudate:

✓ Chorea: Multiple rapid, random movements

### Putamen:

- ✓ The Putamen is the Commonest site for hypertensive hemorrhage
- ✓ Lesion: flicking movements in hands, face and other parts of body---Chorea

### Globus pallidus

✓ Defect in globus pallidus cause Athetosis

### Subthalamic nucleus

✓ Hemiballismus refer to violent projectile movements of limb and typically observed in upper limb contralateral to the involved Subthalamic nucleus, mostly in the hypertensive patient

### Substantia nigra:

- ✓ The Largest nucleus of the midbrain
- ✓ Related with crus cerebri
- ✓ Parkinson disease----loss of pigmented Dopaminergic neurons

### Stratum or Neostriatum

- Multiple small lesion in the Putamen leads to flicking, multiple rapid purposeless quickly jerky involuntary movement—dance like
- **Huntington** disease
  - ✓ show anticipation and genome printing
  - Atrophy of stratum, loss of striatal GABAergic Neurons

### Corpus Stratum

- Neostriatum plus Globus pallidus OR
- Caudate plus lentiform nucleus OR Caudate plus Putamen plus globus pallidus
- Lentiform nucleus-LPG---: Putamen plus globus pallidus
- A Lesion in the globus pallidus lead to spontaneous and often continuous writhing movements in the hands, an arm, or the face, movements called the athetosis

### Parallel Circuit

- -Control of skeletal muscle Skeletomotor loop:--
- -Control of extraocular muscle Oculomotor loop: -
- -Role in cognition Association loop:-
- -Maturation/emotion Limbic loop:--

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### Neuroanatomy, Neurophysiology & Neuropathology

### Treatment:

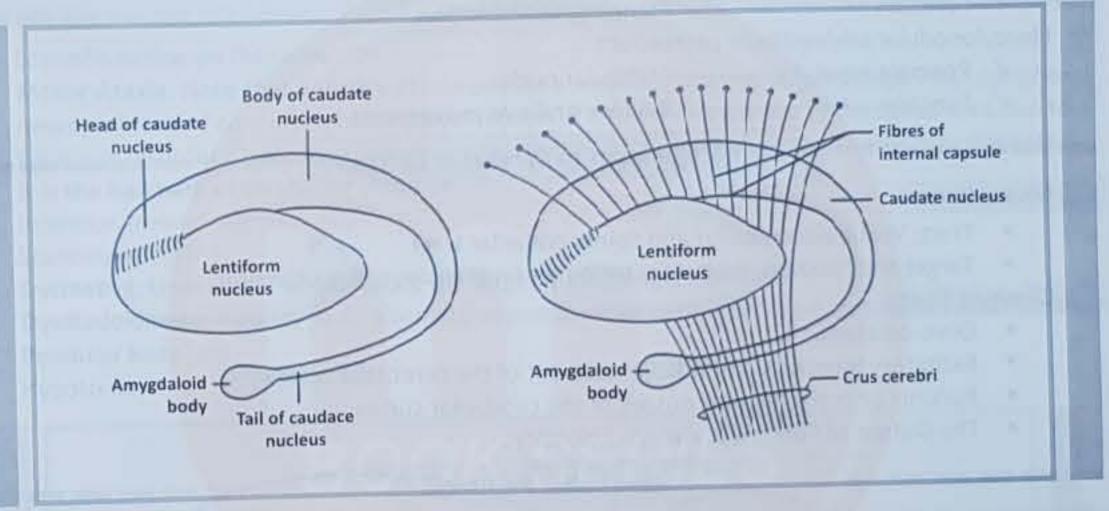
### Carbidopa-levodopa:

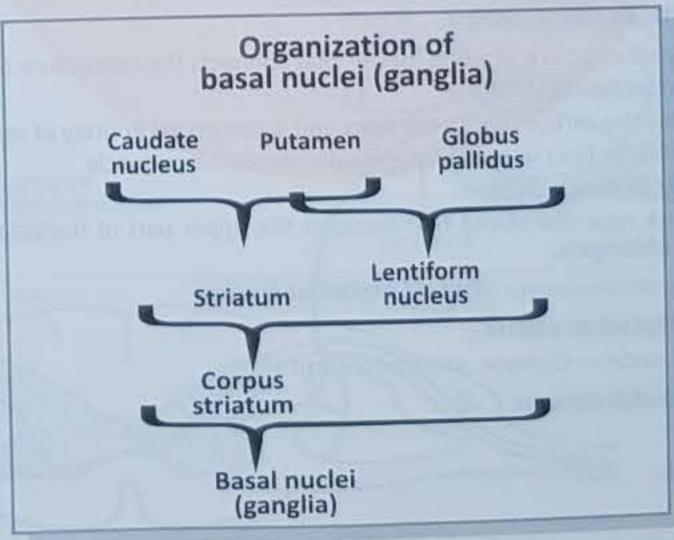
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Neuroanatomy, Neurophysiology & Neuropathology

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- Globose
- Fastigial nucleus-----Most Medial

### Chapter 7

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Neuroanatomy, Neurophysiology & Neuropathology

### The Layers of Cerebellar Cortex

My Personal Garden (from outer to inner side)

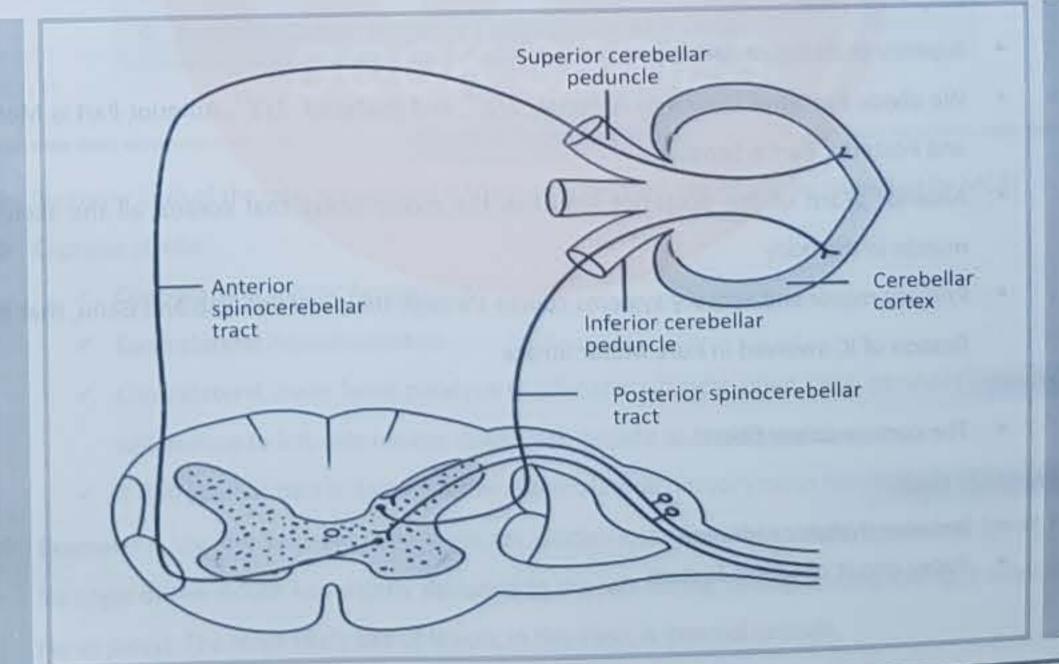
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### Posterior Limb:

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- Optic radiation---- Most Posterior in the Posterior Limb, these are **Projection Fiber**
- Superior thalamic radiation
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- Primary motor and sensory systems course through the posterior limb and Genu, that the Reason of IC Involved in Pure Motor Stroke

### Genu:

The corticonuclear fibers

### Anterior Limb:

- Anterior thalamic radiation
- Papez circuit of Limbic System

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Neuroanatomy, Neurophysiology & Neuropathology

### Retrolentiform:

Posterior thalamic radiation-----Optic radiation

### Sublentiform:

Inferior thalamic radiation------Auditory radiation

### Blood supply of Internal Capsule

Internal capsule	Arterial supply	Tracts
Anterior limb	Medial striate branch of ACA	Thalamocortical
Genu	Lenticulostriate branch of MCA	Corticobulbar
Posterior limb	Lenticulostriate branch of MCA	Corticospinal, all somatosensory thalamocortical projection

### Naseem Sherzad High-Yield Points

- . The main supply of Internal Capsule is MCA
- \* MCA Occlusion -----Contralateral Homonymous Hemianopia
- Pure Motor Stroke------Internal carotid artery
- The Anterior part of Posterior Limb + Genu------Motor
- Posterior Part of Posterior Limb Plus Anterior Limb-----Sensory

### Internal Capsule Stroke

- Posterior limb of the internal capsule is the most common site of stroke (supplied by MCA)
- Capsular stroke:
  - ✓ Contralateral spastic hemiplegia
  - ✓ Contralateral Hemianesthasia
  - ✓ Contralateral lower facial paralysis (explanation, if right-sided facial paralysis occur mouth will deviate to left-side means mouth will deviate to healthy side)
  - ✓ If Retrobulbar part is damaged then Contralateral homonymous hemianopia will result
- \* Example: A seventy-year-old male develops sudden loss of power in right upper and lower limb, his angle of the mouth has slightly deviated to the left during talking (means the right sided facial nerve palsy). The most likely site of lesion, in this case, is internal capsule.

Neuroanatomy, Neurophysiology & Neuropathology

### **Autonomic Nervous System**

### Overview

- Sympathetic and parasympathetic nervous systems belong to the autonomic nervous system.
- Both nervous systems originate from the spinal cord.
- They are composed of pre-ganglionic and post-ganglionic neurons.
- Ganglion: A cluster of interconnecting nerve cells outside the brain.
- . Autonomic ganglia are clusters of neuron cell bodies that transmit sensory signals from the periphery to the integration centers in the CNS.
- In the autonomic nervous system, fibers from the CNS to the ganglion are known as preganglionic fibers.
- . All preganglionic fibers of the ANS are cholinergic meaning they have acetylcholine as their neurotransmitter, and are myelinated for faster transmission.
- Postganglionic fiber: These are the fibers that run from the ganglion to the effector organ.
- In both divisions of the autonomic nervous system, postganglionic neurons express nicotinic acetylcholine receptors to receive signals from Preganglionic neurons.
- . Both nervous systems control the physiological processes of the body (ex: respiration, digestion, circulation, urination, and reproduction). They are involved in maintaining the homeostasis of the body.
- . Cholinergic, meaning they releasing acetylcholine at the synapse in the ganglion

### Sympathetic Nervous System

- Thoracolumbar outflow---Thoraco----T1, Lumbar----L2/L3, so T1-L2/L3
- Preganglionic fibers -----short, cholinergic
- Postganglionic fibers -----long, adrenergic means release of nor-epinephrine, except sweat gland and arrectores pilorum in which postganglionic fibers are cholinergic
- . Another major difference between the two ANS systems is divergence, or the number of postsynaptic fibers a single preganglionic fiber creates a synapse with. Whereas in the parasympathetic division there is a divergence factor of roughly 1:4, in the sympathetic division there can be a divergence of up to 1:20.

### Action:

✓ Fight or flight

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- Catabolic "expend energy"
- Dilate pupil----due to Alpha stimulation
- Stimulates the release of glucose, inhibit insulin release
- ✓ Stimulate secretion of epinephrine and nor-epinephrine from the adrenal gland
- ✓ Increases the rate of glycogen breakdown
- ✓ Dilates the bronchial tubules and inhibits the saliva secretion
- ✓ Increases heartbeat, blood level, and metabolic rate
- ✓ Generates an excitatory homeostatic effect
- ✓ Covers a large area in the body

### Parasympathetic Nervous System

- Cranio 3,7,9,10, sacral ---- \$234 · Cranio-sacral outflow-
- -Long, cholinergic Preganglionic fibers —
- -Short, cholinergic Postganglionic fibers -

### Chapter 7

### Neuroanatomy, Neurophysiology & Neuropathology

### Action:

- ✓ "Feed and Breed" and "rest and digest"
- ✓ Constricts the bronchial tubules
- ✓ No action on the adrenal gland and No effect on the glycogen breakdown
- Stimulate the secretion of saliva (promote the secretion of different gland associate with alimentary tract), and relaxation of the fundus of the stomach
- ✓ It Decreases heartbeat, blood level, and metabolic rate.
- Generates an inhibitory homeostatic effect
- Covers a small area in the body

#### Adrenal Medulla

### A modified part of the sympathetic nervous system

- \* Receive stimulation via acetylcholine to release catecholamines such as epinephrine and norepinephrine
- Chromaffin cells function as modified post-ganglionic nerves. Instead of releasing epinephrine and norepinephrine into a synaptic cleft, cells of the adrenal medulla release these catecholamines into the bloodstream as hormones
- Adrenal medulla is directly connected to the Preganglionic fiber
- Preganglionic sympathetic fiber synapse on the chromaffin cell of the adrenal medulla at nicotinic receptors in adrenal medulla and secrete acetylcholine, which activates the secretion of epinephrine and to lesser extent nor-epinephrine from it and is released into circulation.

### **Dual Autonomic Innervation**

### Reciprocal system:

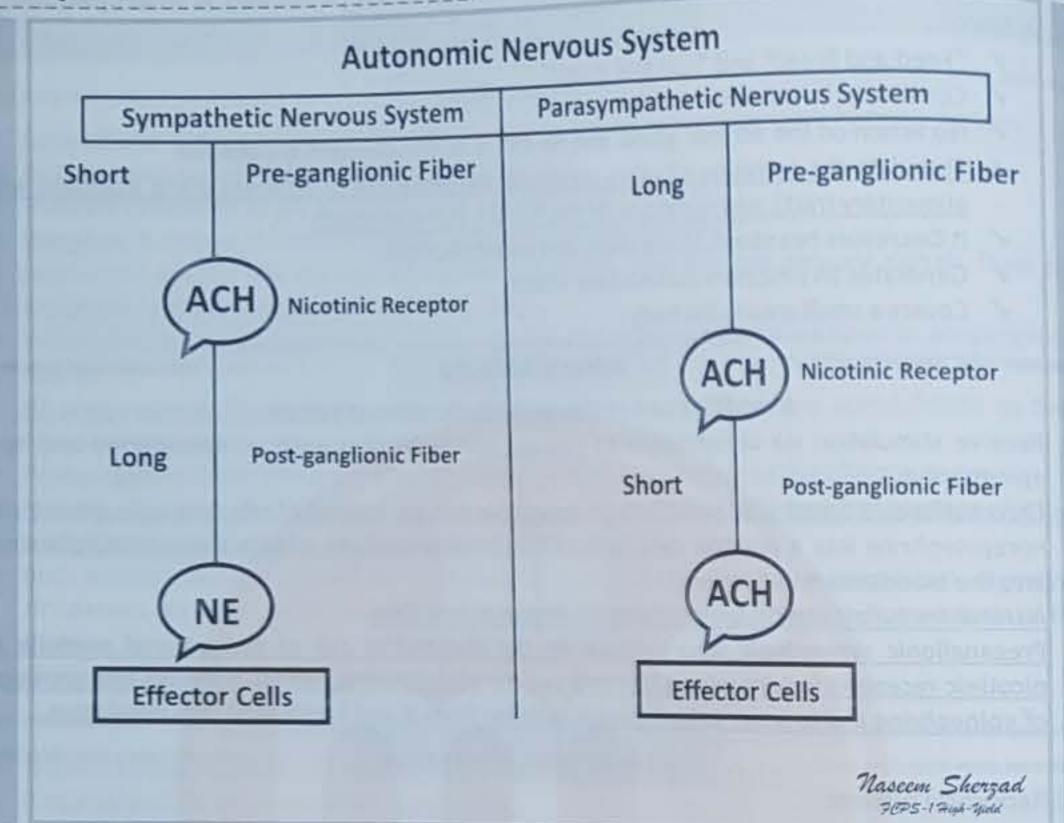
- ✓ One system inhibits while the other stimulates activity of the target organ.
- ✓ Very fine control of organ function (think of gas and break pedal).
- ✓ In general, it produces opposite effects in a particular organ.
- Example: control of HR and intestinal motility (very fine control of organ function)
- ✓ What does the reciprocal effect allow the body to do?
  - Dual innervation of organs by both branches of ANS allows precise control over the organ's activity
- . What are the exceptions to the general rule of dual reciprocal innervation by the two branches of the autonomic nervous system?
  - ✓ Most sweat glands are innervated only by sympathetic nerves. The preganglionic fibers of these nerves are unusual because they secret ACH rather than Nor-epinephrine
  - ✓ Most arterioles and veins receive only sympathetic nerve fibers (arteries and capillaries) are not innervated)
  - ✓ Salivary gland are innervated by both autonomic divisions, but unlike elsewhere, sympathetic and parasympathetic activity is not antagonist, but stimulate salivary secretion. Dual nerve supply but not reciprocal and not antagonist
- · Organ with only sympathetic innervation: adrenal medulla, Arrector pilli, sweat gland and blood vessels of skin

### Cooperative Effect:

- ✓ Promote the same goal.
- ✓ Example of cooperative effect: Salivary gland secretion, lacrimal gland secretion, and male sexual response

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Neuroanatomy, Neurophysiology & Neuropathology



### The Pattern of Distribution of the Sympathetic fibers

Spinal segment	Sympathetic Innervation	Destination
T1-2	Via internal carotid and vertebral arteries	Head and neck, ciliary muscle and iris, Blood vessels, Sweat glands
T1-4	Via cardiac and pulmonary plexuses	Heart and lower respiratory components like Bronchia
T2-7		Upper limb
T4-L2	Via coeliac, mesenteric, hypogastric and pelvic plexuses	Adrenal medulla, Alimentary tract, colon and rectum, bladder and genitalia
T11-L2		Lower limb

Neuroanatomy, Neurophysiology & Neuropathology

### Prototypes of Drugs that affect Autonomic Activity

Type of receptors	Agonist	Antagonist
Adrenergic		
α1	<ul> <li>Norepinephrine</li> <li>Phenylephrine</li> </ul>	<ul><li>✓ Phenoxybenzamine</li><li>✓ Phentolamine</li><li>✓ Prazosine</li></ul>
α	- Clonidine	✓ Yohimbine
β <sub>1</sub>	<ul> <li>Norepinephrine</li> <li>Isoproterenol</li> <li>Dobutamine</li> </ul>	✓ Propranolol ✓ Metoprolol
β2	<ul><li>Isoproterenol</li><li>Albuterol</li></ul>	✓ Propranolol ✓ Butoxamine
Cholinergic		
Nicotinic	✓ Ach ✓ Nicotine ✓ Carbachol	✓ Curare ✓ Hexamethonium
Muscarinic	✓ Ach ✓ Muscarine, Carbachol	✓ Atropine

### Adrenergic Receptors

α1	<ul> <li>Vasoconstriction</li> <li>Increase peripheral resistance</li> <li>Increase blood pressure</li> <li>Mydriasis</li> <li>Increased closure of internal sphincter of the bladder</li> </ul>
α2	<ul> <li>Inhibition of nor-epinephrine release</li> <li>Inhibition of acetylcholine release</li> <li>Inhibition of insulin release</li> </ul>
β1	<ul> <li>Tachycardia</li> <li>Increased lipolysis</li> <li>Increased myocardial contractility</li> <li>Increased release of renin</li> </ul>
β2	<ul> <li>Vasodilation and Bronchodilation</li> <li>Increase liver and muscle glycogenolysis</li> <li>Increase release of glucagon</li> <li>Relaxed urinary smooth muscle</li> </ul>

Neuroanatomy, Neurophysiology & Neuropathology

Neurons

Axon:

Carry impulses away from the cell body

Dendrites:

Carry impulses toward the cell body

Classification according to the number of processes

Unipolar neuron:

✓ Have only one process which functions as axon

✓ e.g. only in the mesencephalic nucleus of 5<sup>th</sup> cranial nerve

Bipolar neuron:

✓ Have two processes which arises from the opposite pole of the cell body, one particular telegraphics. dendrite while other is an axon

Pseudo-polar neuron:

✓ They have a single process which divided into two branches close to the cell body.

✓ e.g. Dorsal root ganglion

Multipolar neuron:

✓ They have a single axon and multiple dendrites e.g. pyramidal cell of cerebral cortex

Axon Hillock

It is a region of cell body where axon originates or axon Hillock situated between the cell body and axon

The action potential, which begins at the axon hillock, is an electrical impulse that travels down the axon toward the terminal button. The action potential operates on an "all-ornone" principle meaning the axon hillock either create an action potential or does nothing

NissI granules are absent in axon hillock

Having a lower threshold than the rest of axon

Having high sodium channel concentration

Nissl granules:

✓ They are granules present in the cytoplasm of the cell body, except in axon hillock

✓ They are composed of RNA and involved in protein synthesis and utilize them during neuron activity

The Node of Ranvier:

 The node of Ranvier is a collar of naked axon between a proximal and distal bundle of myelin that has Myelinated the axon

The node of the ranvier are sites that permit action potential to jump from node to node

Saltatory conduction dramatically increase the conduction velocity of impulse in

Layer of Neuron:

Epineurium: The outermost layer of dense irregular connective tissue surrounding a

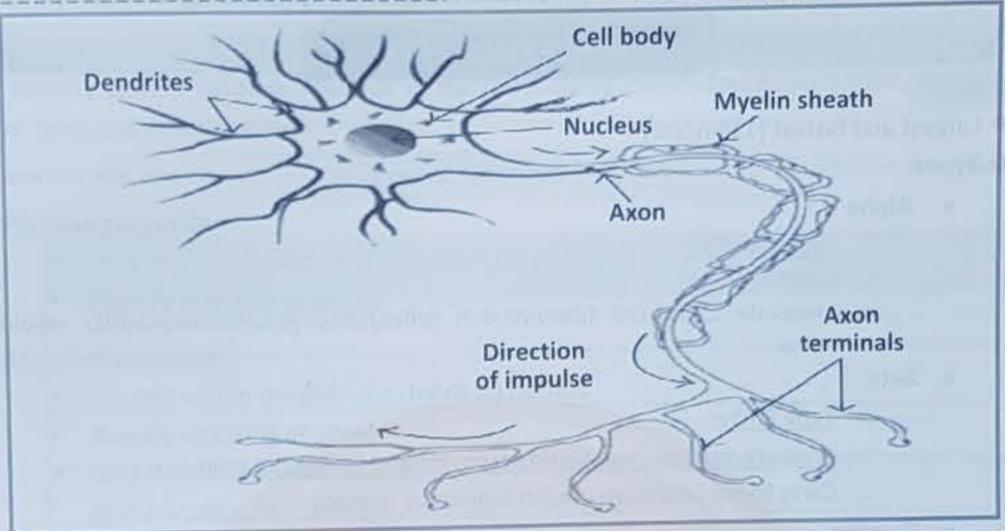
Perineurium: The connective tissue sheath surrounding each bundle (fascicle) of nerve

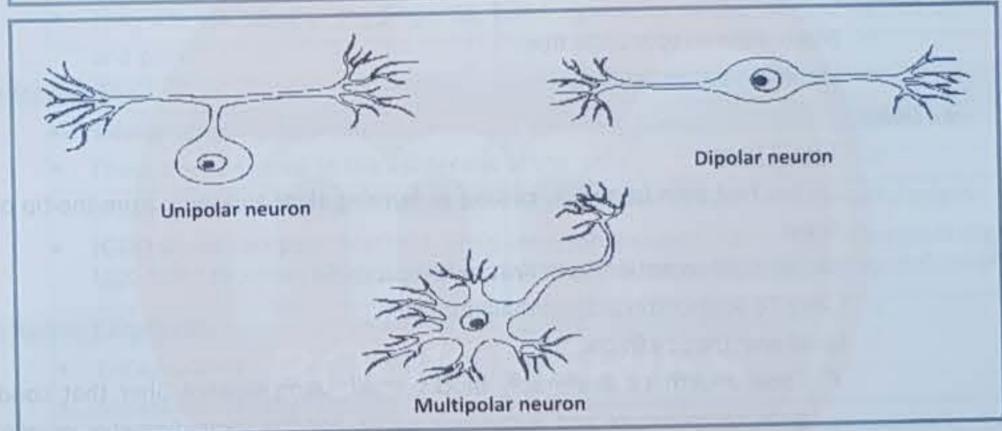
Endoneurium: A layer of delicate connective tissue made up of endoneurial cells that

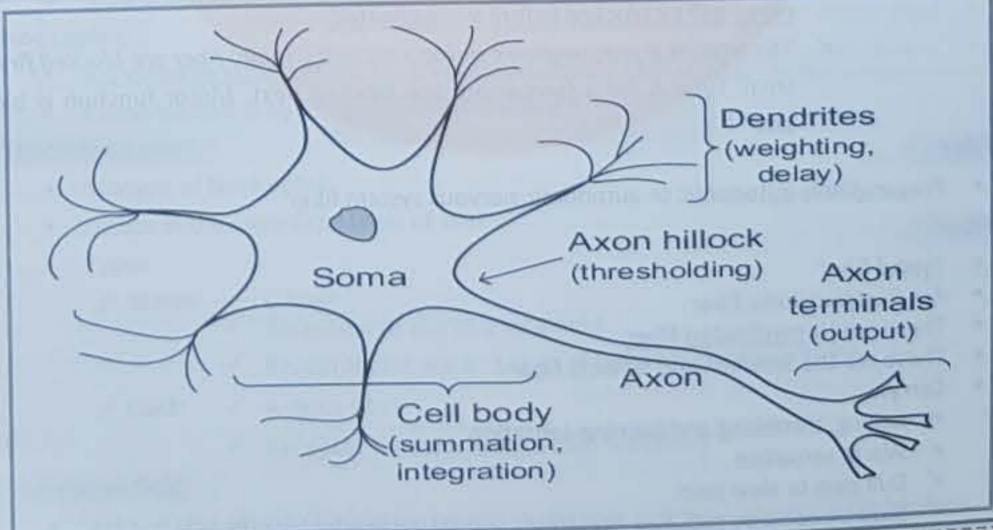
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Neuroanatomy, Neurophysiology & Neuropathology

### NERVE FIBER TYPES



#### 1) A Fiber:

- Largest and fastest (130m/sec)
- · Types:
  - Alpha

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- Type one fiber
- o UMN
- o Innervate Extrafuasi fiber/stretch reflex/knee jerk/monosynaptic/ involuntary reflex
- Beta:
  - Type 2 fiber
  - Pressure and touch sensation from tip and lip but not pain
  - Carry to dorsal Colum medial lemniscus system
- Gamma
  - Motor neuron to muscle fiber
  - o Innervate Intrafusal fiber
- Delta
  - o Type 3 fiber
  - O Carries Fast pain (pinprick, cutting or burning skin) and temp from the tip of the finger
  - Carries Cold sensation form Krause receptors
  - Carry To anterolateral Spinothalamic tract
  - Local anesthetic effects:
    - ✓ Local anesthetic preferably blocks small, unmyelinated fiber that conducts. pain, temperature and autonomic nerve. For the same diameter, myelinated nerve will be blocked before unmyelinated.
    - ✓ The smaller B preganglionic autonomic and C (pain) fiber are blocked first, the small Type A-delta (sensation) are blocked next. Motor function is blocked last
- 2) B Fiber:
  - Preganglionic autonomic or autonomic nervous system fiber
- 3) C Fiber:
  - Type 4 fiber
  - Are Postganglionic fiber
  - These are Unmyelinated fiber
  - These are the Smallest and slowest fiber
  - Carry:
    - ✓ Itching, throbbing and burning sensation
    - √ Warm sensation
    - Dull pain or slow pain
    - ✓ Stop bleeding by reducing pressure —sensation carries by c- fiber

Chapter 7 Neuroanatomy, Neurophysiology & Neuropathology

The sensory system develop in uterus in the in following order: Touch, vestibular, smell, hearing, Receptive helds are large vision, taste and proprioception

Type of Mechanoreceptors Receptive fields are small

Pacinian corpuscle:

8 0 0 x 2

- Sensation: High-frequency vibration(256), tapping of an appendi
- Rapidly adapting or phasic

Meissner corpuscle:

- Located within the glabrous (hairless) dermis
- Rapidly adapting or phasic

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- (128 Hz), two-point Sensation: Stimulated by low-frequency vibration discrimination/tactile two-point discrimination,
- They are abundant in the fingertip, hand, eyelid, tip of the tongue, nipples, soles, clitoris and penis

- Merkel disc recogning Receptors Slowly Adapting Recogning Recognition Slowly adapting or tonic
  - These discs lie deep in the epidermis of the skin
  - Sense----Pressure, position, deep static touch features such as shapes and edges
  - IGGO Dome receptor: Merkel's discs are often grouped together in a receptors organ call the Iggo dome receptor, which projects upward against the underside of the epithelium of the skin
- Ruffini Corpuscle India v basta a touted w double one deane, and touted virtaming
  - Encapsulated

of the stimulus

- Sensation: Steady Pressure
  - Slow adapting or tonic

Pacinian corpuscie Light touch

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- Nociceptor:
  - Activated by strong pressure, severe cold, severe heat or chemicals
  - Response to it is by flexor withdrawal reflex
- Thermoreceptors
  - Subtype of Nociceptor
  - Locate in the superficial layer of skin
  - Types

- Reception of warm is long field
- ✓ Receptors for warm: organ of Golgi Mazzoni and Ruffini rendons at either end of the muscle,
  - √ A-delta fiber ✓ Receptor for cold: Krause bulb receptors ₽ Cold:
- serve a sure sensory function. There are two types of intrational Receptive field:
  - Area of skin whose stimulation results in changes in firing rate of sensory neurons

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- The Area varies inversely with density of sensory receptors e.g.
  - Back and leg have low-density of receptors
    - Receptive fields are large
  - √ Fingertips have high-density of receptors
    - Receptive fields are small

Receptors Types	Adequate Stimulus	
Mechanoreceptors	Mechanical displacement	
Thermoreceptors	Temperature changes	
Nociceptor	Pain	
Chemoreceptors	Chemical	
Photoreceptors	Light	

Rapidly Adapting Receptors	Slowly Adapting Receptors
<ul> <li>Phasic receptors</li> </ul>	<ul> <li>Tonic receptors</li> </ul>
<ul> <li>Show decline in action potential frequency with time in response to a constant stimulus</li> </ul>	<ul> <li>Respond repetitively to prolonged stimulus</li> </ul>
Primarily detect the onset and offset     of the stimulus	Detect a steady stimulus
<ul> <li>Pacinian corpuscle</li> <li>Light touch</li> <li>A-delta type II fiber (fast pain)</li> </ul>	<ul> <li>Muscle spindle, pressure, slow pain</li> <li>C-fiber (slow pain)</li> <li>A-delta type I fiber</li> </ul>

### **Types of Muscle Fibers**

### Extrafuasl fiber

- · Form Bulk of muscle
- Alpha motor neurons

### Intrafusal fiber

- The intrafusal fibers are positioned in parallel to the extrafusal fibers (the regular) contractile units of the muscle) with the ends of the spindle capsule attached to the tendons at either end of the muscle.
- Intrafusal fibers do not contribute to the overall contractile force of the muscle, but rather serve a pure sensory function. There are two types of intrafusal fibers in mammalian muscle spindles. The first type contains many nuclei in a dilated central area and is called a

nuclear bag fiber. There are two subtypes of nuclear bag fibers, dynamic and static. Typically, there are two or three nuclear bag fibers per spindle. The second intrafusal fiber type, the nuclear chain fiber, is thinner and shorter and lacks a definite bag. Each spindle has about five of these fibers.

- Gamma motor neurons
- Types
  - ✓ Nuclear bag fiber
    - O Detect change in length, fast dynamic change
    - Increase impulse generation
  - √ Nuclear chain fiber
    - O Detect static change in muscle length

### Type of Muscle Reflexes

### Muscle stretch reflex

- The stretch reflex is a <u>muscle contraction</u> in <u>response to stretching</u> within the muscle
- Myotic reflex or knee jerk reflex
- Monosynaptic
- Group 1a alpha motor neuron
- Maintain the length of the muscle
- Cause contraction in the muscle that was stretch
- Examples
  - ✓ Jaw jerk reflex (CN V)
  - ✓ Biceps reflex C5/C6.

### Inverse stretch reflex

Up to a point, the harder a muscle is stretched, the stronger is the reflex contraction. However, when the tension becomes great enough, contraction suddenly ceases and the muscle relaxes. This relaxation in response to strong stretch is called the inverse stretch reflex or autogenic inhibition.

The receptor for the inverse stretch reflex is in the Golgi tendon organ. This organ consists of a netlike collection of knobby nerve endings among the fascicles of a tendon. There are 3-25 muscle fibers per tendon organ. The fibers from the Golgi tendon organs make up the lb group of myelinated, rapidly conducting sensory nerve fibers. Stimulation of these Ib fibers leads to the production of IPSPs on the motor neurons that supply the muscle from which the fibers arise. The Ib fibers end in the spinal cord on inhibitory interneurons that in turn terminate directly on the motor neurons. They also make excitatory connections with motor neurons supplying antagonists to the muscle.

- Inverse Myotic reflex
- Di-synaptic

separate axons

are the smallest cell in CNS

3) Schwann cell:

- \* Transmit information regarding Tendon Tension and the rate of change of tension
- \* Tendon jerk are clinically examined to assess the integrity of the reflex pathway
- Clonus: A characteristic of states in which increased -motor neuron discharge is present is clonus. This neurologic sign is the occurrence of regular, repetitive, rhythmic contractions of a muscle subjected to sudden, maintained stretch. Only sustained clonus with five or more beats is considered abnormal. Ankle clonus is a typical example. Clonus may also occur after disruption of descending cortical input to a spinal glycinergic inhibitory interneuron called the Renshaw cell. This cell receives excitatory input from -motor neurons via an axon collateral (and in turn it inhibits the same). Renshaw cells are inhibitory interneurons found in the gray matter of the spinal cord. Located in the anterior or ventral horn in close association with motor neurons

### Flexor withdrawal reflex

The withdrawal reflex is a typical polysynaptic reflex that occurs in response to a usually painful stimulation of the skin or subcutaneous tissues and muscle. The response is flexor muscle contraction and inhibition of extensor muscles, so that the body part stimulated is flexed and withdrawn from the stimulus. When a strong stimulus is applied to a limb, the response includes not only flexion and withdrawal of that limb but also extension of the opposite limb. This crossed extensor response is properly part of the withdrawal reflex. Strong stimuli in experimental animals generate activity in the interneuron pool that spreads to all four extremities. This is difficult to demonstrate in normal animals but is easily demonstrated in an animal in which the modulating effects of impulses from the brain have been abolished by prior section of the spinal cord (spinal animal). For example, when the hind limb of a spinal cat is pinched, the stimulated limb is withdrawn, the opposite hind limb extended, the ipsilateral forelimb extended, and the contralateral forelimb flexed. This spread of excitatory impulses up and down the spinal cord to more and more motor neurons is called irradiation of the stin ilus, and the increase in the number of active motor units is called recruitment of motor units.

number of active motor units is called recruitment of motor units.

number of active motor units is called recruitment of motor units.

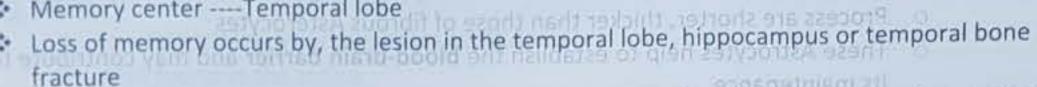
- The withdrawal reflex (nociceptive flexion reflex or flexor withdrawal reflex) is a spinal reflex intended to protect the body from damaging stimuli, and no squal to not production of
- Poly-synaptic (many different muscle may be called to play) lenigs ent in bine stedit di
  - Protective reflex and important for survival violations salar make exertation and motor motor neurons. They also make excitatory
  - Group 3,4,5 fiber

Fage 121:

- Flexion on ipsilateral side and extension on the opposite side in a stroyth acreym and to the muscle.
- Present at birth, persist throughout life
- ----abdominal reflex, cremasteric reflex Poly-synaptic---

Memory center --- Temporal lobe

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Bilateral hippocampus lesion cause anterograde amnesia, loss of ability to encode events of recent past in long term memory Found most abundant in white marrer

Bilateral mammillary bodies lesion cause retrograde plus anterograde amnesia

### Types of memory:

### Long term memory

- ✓ Involved structural changes and made by protein synthesis and made by protein synthesis.
- Long term memory need anatomical changes and work (and miles and a less and a
- Conversion of short term memory to long term memory occurs in the hippocampus

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- Bilateral lesion of hippocampus block the ability to form new long term memories
- OE TO STREET Corpus striatum is important for long term memory, intelligence and IQ development

#### Short term memory:

- ✓ Short term memory need synaptic changes
- ✓ Short term memory loss occurs due to lesion in the mammillary body One Stinwant myelinate single internodal segments of a single axon

### Histology

### Neuroglia

The supporting cell of CNS are called Neuroglia

### Two types:

- Neuroglia proper: three types of cells, Astrocytes, Olgiodendryocytes and microglia
- Ependyma: consist of Ependymal cell that line that cavities in brain and spinal cord

### 1) Astrocytes:

- Astrocytes are the largest of the neuroglial cell
- The most abundant type of macroglial cell in CNS, have a large number of radiating processes bon theig apaint SNO a to levivous to someth and something processes S THAT BLE
  - Astrocytes get their name because they are "star-shaped".
- Astrocytes hypertrophy and proliferate after an injury to the CNS, they fill up the extracellular space left by degenerating neurons by forming an astroglial scar
  - Nervous system repair: Upon injury to nerve cells within the central nervous system, Astrocytes fill up the space to form a glial scar, and may contribute to neural repair.
- Radial glia are precursors of Astrocytes that guide neuroblast migration during CNS development Regeneration capacity present in Asterocytes assessed to revisit anivirability and

  - Astrocytes and pericytes are found at the blood-brain barrier outside the basal lamina (a
- Astrocytes have processes with "end feet" that cover more than 95% of the basal lamina adjacent to the capillary endothelial cells noxe tuo and mont alungs lutassoous guided by Schwann cell back to their target

Page | 21d

- Regeneration proceeds at the rute of 1-2mig-day vehace of slow Protoplasmic Asterocytes PG 10 store of slow and slow a
  - o Found most abundant in Gray matter and have branched process that envelop blood vessels

· DISYNAPHO

- Protoplasmic are the most prevalent
- Contain some intermediate filaments composed of glial fibrillar acidic protein
- O Process are shorter, thicker than those of fibrous Asterocytes
- o These Astrocytes help to establish the blood-brain barrier and may contribute to its maintenance

### ✓ Fibrous Astrocytes:

- Found most abundant in white matter
- Contain many intermediate filaments
- o Form scar tissue in CNS

### 2) Oligodendrocyte:

- Form myelin in CNS (brain and spinal cord)
- Located in both gray and white matter
- Each cell produce myelin for several axons
- These hindering or inhibit regeneration of cut central axon
- Each Oligodendrocyte can myelinate individual intermodal segments of an average of 30 separate axons

### 3) Schwann cell:

- Schwann cell are supporter cell in the peripheral nervous system
- One Schwann myelinate single internodal segments of a single axon
- A mesaxon is a pair of parallel plasma membranes of a Schwann cell, marking the point of edge-to-edge contact by the Schwann cell encircling the axon.

### 4) Microglia:

- They are small elongated cell with rod-shaped, condensed nucleus
- Found in both white and gray matter
- Microglia proliferate and migrate to the site of CNS injury and phagocytose neuronal debris after injury
- Activated microglial cells become antigen-presenting cells and secret cytokines. Microglia are the smallest cell in CNS
- Pericytes are the microglia that contribute to the blood-brain barriers
- Microglia determine the chance of survival of a CNS tissue graft and are the cells that are targeted by the HIV-1 virus in a patient with AIDS

### Ependymal cell:

- These are epithelial cells (simple Cuboidal) that line the cavities of the brain and spinal cord. Apical surface possesses Microvilli
- Modified ependymocytes line choroid plexus
- Unlike epithelia, however, Ependymal cells do not rest on a basement membrane but, rather, the bases of the cells taper and then branch into fine process which ramify within the underlying layer of process derived from Astrocytes

### 6) High Yield Points:

- Neurons with severed axons in the PNS are capable of complete axonal regeneration.
- Successful sprouts from the cut axon grow into and through endoneurial sheath and are guided by Schwann cell back to their target
- Regeneration proceeds at the rate of 1-2mm/day, which corresponds to the rate of slow anterograde transport
- Myelination in fetus start at 4 months of fetal life

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### Neurotransmitter

### GABA:

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- It is formed by decarboxylation of Glutamate
- Also found in the retina

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- The Neurotransmitter of corticostriatal fiber
- Most common Inhibitory neurotransmitter of CNS
- Anxiety decreased by activation of GABA receptors
- Flickering movements are caused by decrease in GABA level

### Endorphins:

- Natural painkiller
- Beta-endorphins is found in the neurons of hypothalamus, as well as the pituitary gland

### Serotonin:

- Pain inhibitor, Mood control, sleep
- Aggression
- The raphe nuclei are the primary location in the brain for the production of the neurotransmitter serotonin

### Dopamine:

- Both excitatory and inhibitory neurotransmitter
- Function-----Learning, pleasure, emotion
- Regulate prolactin
- Secreted by nigrostriatal pathway

### @ Glutamate:

- Does not cross blood-brain barrier
- The Most common excitatory neurotransmitter of CNS
- Present In rod and cones

### Melatonin:

- The Level peak in deep sleep
- Synthesis from serotonin
- Keep the body on time clock
- Inhibit GnRH from the hypothalamus

### Nor-epinephrine/nor-adrenalin

- Non-shivering thermogenesis can produce heat in response to cold stress. This type of thermogenesis is stimulated by the sympathetic nervous system, which release of norepinephrine and epinephrine
- synthesis brain coeruleus is The locus principal of norepinephrine (noradrenaline). Activation of this center produce REM sleep
- Epinephrine or adrenalin acts both as a hormone and neurotransmitter
- In humans, mild core hyperthermia also increase the ante-cubital venous level of norepinephrine but not the adrenaline
- The Hormone that converts norepinephrine to epinephrine is cortisol

### Enzyme for degradation:

- MAO: Epinephrine+ nor-epinephrine and Serotonin
- COMT: Epinephrine + nor-epinephrine and Dopamine

### Summary

- There are two main types of microglia and macroglia. Microglia are scavenger cells. Macroglia include oligodendrocytes, Schwann cells, and astrocytes. The first two are involved in myelin formation; astrocytes produce substances that are tropic to neurons, and they help maintain the appropriate concentration of ions and neurotransmitters.
- Neurons are composed of a cell body (soma) which is the metabolic center of the neuron, dendrites that extend outward from the cell body and arborize extensively, and a long fibrous axon that originates from a somewhat thickened area of the cell body, the axon hillock.
- The axons of many neurons acquire a sheath of myelin, a protein-lipid complex that is wrapped around the axon. Myelin is an effective insulator, and depolarization in myelinated axons jumps from one node of Ranvier to the next, with the current sink at the active node serving to electrotonically depolarize to the firing level the node ahead of the action potential.
- Orthograde transport occurs along microtubules that run the length of the axon and requires molecular motors, dynein, and kinesin.
- Two types of physicochemical disturbances occur in neurons: local, non-propagated potentials (synaptic, generator, or electrotonic potentials) and propagated potentials (action potentials).
- ❖ In response to a depolarizing stimulus, voltage-gated Na<sup>+</sup> channels become active, and when the threshold potential is reached, an action potential results. The membrane potential moves toward the equilibrium potential for Na<sup>+</sup>. The Na<sup>+</sup> channels rapidly enter a closed state (inactivated state) before returning to the resting state. The direction of the electrical gradient for Na<sup>+</sup> is reversed during the overshoot because the membrane potential is reversed, and this limits Na<sup>+</sup> influx. Voltage-gated K<sup>+</sup> channels open and the net movement of positive charge out of the cell helps complete the process of repolarization. The slow return of the K<sup>+</sup> channels to the closed state explains after-hyperpolarization, followed by a return to the resting membrane potential.
- Nerve fibers are divided into different categories based on axonal diameter, conduction velocity, and function.
- Neurotrophins are produced by astrocytes and transported by retrograde transport to the neuronal cell body, where they foster the production of proteins associated with neuronal development, growth, and survival.
- Anterior cord syndrome: Anterior spinal cord syndrome involves complete motor paralysis and loss of temperature and pain perception distal to the lesion. Since posterior columns are spared, light touch, vibration, and proprioceptive input are preserved. This syndrome is caused by compression of the anterior spinal artery, which results in anterior cord ischemia or direct compression of the anterior cord. It is associated with burst fractures of the spinal column with fragment retropulsion caused by axial compression.
- Posterior cord syndrome: injury to the posterior spinal cord affecting the posterior column (fine touch, vibration, pressure and proprioception). Caused by occlusion of posterior spinal artery.

  There is ipsilateral loss of vibration and proprioceptive sensation below the lesion

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### Important Tables

### **Rigidity Types**

Туре	Condition in which occurs
Clasp-knife rigidity	UMN lesion
Cogwheel rigidity	Parkinson disease
Lead pipe rigidity	Parkinson disease
Drugs that abolish rigidity	Chlorpromazine and Procaine

### White Matter of Cerebral Hemisphere

Commissure fibers	Projection fibers	Association fibers
Connect corresponding gyri of the two cerebral hemisphere Example  Corpus callosum: connects	Connect more or less vertically, efferent fibers from cerebral cortex to subcortical	<ul> <li>Connect one gyri to another in the same hemisphere</li> </ul>
the two cerebral hemisphere and continuous at the occipital lobe as forceps major  Fornix: white matter tract connects hippocampus to hypothalamus and prefrontal cortex  Anterior commissure	Connect the cerebral cortex with the thalamus, Pons and spinal cord  Example:  ✓ Internal capsule  ✓ Optic radiation	

### Upper motor neuron lesions and lower motor neurons lesion

<u>U</u> MN lesions	<u>L</u> MN lesions
Weakness	Weakness
No atrophy	Atrophy
No fasciculation	Fasciculation
Toneincreased	Tonedecreased
Reflexesincreased	Reflexesdecreased
Babinski's signpositive	Babinski's signnegative
Spastic paralysis	Flaccid paralysis
Clasp-knife spasticity	No Clasp-knife spasticity

NOTE: UMN-----Everything up, LMN-----Everything down

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### Embryology

Primary vesical	Secondary vesical	Adult Derivatives
Prosen-cephalon	Telen-cephalon	Cerebral hemisphere, Hippocampus, olfactory bulb, caudate, Putamen, cavities: lateral ventricle
	Dien-cephalon	Thalamus, hypothalamus, mammillary bodies, pineal gland, Neurohypophysis, optic Chiasma, optic tract, optic nerve, retina, iris, ciliary body, cavities: 3 <sup>rd</sup> ventricles
Mesen-cephalon	Mesen- cephalon	Midbrain (Mesen-cephalon is the first vesical appear), cavities: Aqueduct
Rhomben-cephalon	Meten- cephalon Mylen- cephalon	Pons and cerebellum  Medulla

### Important Centers

Location	Centre
Medulia	<ul> <li>Vasomotor center</li> <li>Respiratory center</li> <li>Swallowing center</li> <li>Coughing center</li> <li>Vomiting center</li> </ul>
<u>P</u> ons	Penumotaxic center
HypoThalamus	Thirst and Satiety center     Temperature regulation center
Chemoreceptor trigger zone(CTZ)	<ul> <li>CTZ is an area of the medulla that communicate with the vomiting center to initiate vomiting</li> <li>CTZ is physiologically outside BBB</li> <li>CTZ contains Opioids receptors, D2 receptors. 5HT3</li> </ul>
Micturition center	<ul> <li>Pons (Guyton Physiology, Page 310, 11<sup>th</sup> edition)</li> <li>Midbrain (BRS Physiology, Page 36, 6<sup>th</sup> edition)</li> </ul>

Chapter 7

Neuroanatomy, Neurophysiology & Neuropathology

### Neuropathology

### HIGH YIELD POINTS

- 1) Multiple sclerosis is the <u>most common demyelinating disorder</u>. It is due to autoimmune destruction of CNS myelin and Olgiodendryocytes.
- 2) Duchenne Muscular dystrophy: Patients do not produce dystrophin but still there is an enlargement of the calf muscle, which is termed as pseudo-hypertrophy. This pseudo-Hypertrophy occurs because of proximal muscle wasting which is an important early physical finding. Death occurs from respiratory insufficiency.
- 3) Lewy bodies are cytoplasmic inclusion of degenerating neuron of the substantia nigra and pars compacta, evident in patients with Parkinson's disease.
- 4) Metachromatic leukodystrophy is the <u>most common leukodystrophy</u> caused by the <u>deficiency of</u> <u>arylsulfatase</u>. Myelin can't be degraded and accumulates in lysosomes.
- 5) The most common solid tumors in children are CNS tumors.
- 6) In adult, the majority of the intracranial tumors are supratentorial.
- 7) In children, the majority of the intracranial tumors are infratentorial.
- 8) Leukemia is the most frequent malignancy in children; CNS tumors are the 2<sup>nd</sup> most common form of malignancy in children.
- 9) The most common posterior cranial fossa tumor in children is Cerebellar Astrocytoma.
- 10) Metastatic tumors to the brain are found more frequently than primary intracranial neoplasm.

  Lung tumor is the most common that metastasis to brain
- 11) MELAS syndrome histological finding is red ragged fibers
- 12) Most common tumor associated with type-1 neurofibromatosis is optic nerve Glioma
- 13) The term post-traumatic epilepsy refers to seizure occurring many years after head injury
- 14) Neuroblastoma Cause opsoclonus myoclonus syndrome
- 15) The most common cause of intracranial hemorrhage is hypertension

### **Brain Abscess**

- Most common route------------Hematogenous root
- Most common lobe involved -----Frontal lobe
- Most common organism causing brain abscess----Streptococci
- Most common agent in penetrating injury------Staphylococcus aureus
- CT-scan: Ring enhancing lesion with a low-density core

Chapter 7 Neuroa

Neuroanatomy, Neurophysiology & Neuropathology

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# Myasthenia Gravis Vs Lambert Eaten Syndrome

### Myasthenia gravis is autoimmune disease caused by antibody (IgG) directed against post-synaptic acetylcholine receptors.

**Myasthenia Gravis** 

- In Myasthenia gravis weakness is aggravated with activity as the day progress
- Myasthenia gravis is associated with Thymomic hyperplasia in 60% and 20% with Thymoma and intermittent Diplopia is a classic sign in myasthenia gravis
- Single-fiber electromyography (SFEMG) is the <u>most sensitive</u> diagnostic test for MG.
- test for the diagnosis of MG measures the serum concentrations of Anti-AChR antibodies and is highly specific for myasthenia gravis. For all practical purposes, this can be considered a gold standard because false positive results are exceedingly rare.

### **Lambert Eaten Syndrome**

Lambert Eaten syndrome is caused by an antibody directed against pre-synaptic calcium channel in neuromuscular junction

In Lambert Eaten syndrome weakness, improve with activity but not with rest.

### Guillen-Barre' syndrome (GBS)

- Guillen-Barre' syndrome (GBS) is the most common cause of acute peripheral neuropathy.
- Guillen-Barre syndrome and polio causing ascending paralysis, while botulism toxin and myasthenia gravis causing descending paralysis
- Guillen-Barre' syndrome is associated with infection like <u>Campylobacter jejuni</u> (most common), cytomegalovirus, Epstein-Barr virus and mycoplasma pneumonia.

### Glioblastoma Multiform

- It is the <u>most common</u> and the most aggressive primary intracranial malignancy in adults and it can cross the midline.
- Characteristic histological features: <u>areas of necrosis</u> surrounded by rows of Neoplastic cells
- Pseudopalisade tumor cell arrangement
- The current WHO classification of primary brain tumors List GBM as a grade IV Astrocytoma

### Astrocytoma

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The most common neurological tumor is Astrocytoma

Grade 1: Pilocytic Astrocytoma

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- Grade 2: Fibrillary Astrocytoma
- Grade 3: Astrocytoma are called Anaplastic Astrocytoma
- Grade 4: Astrocytoma are called glioblastoma multiform

### Meningioma



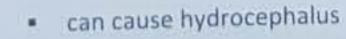
- It is the 2<sup>nd</sup> most common and schwannoma is the 3<sup>rd</sup> most common primary intracranial neoplasm.
- Gross: Attached to the dura, pushes the underlying brain without invasion
- Microscopic:
  - ✓ Meningioma cells are relatively uniform, with a tendency to encircle one another, forming whorls or fascicles pattern
  - ✓ <u>Psammoama bodies</u> (laminated calcific concretions) are frequent.
  - ✓ The cells are spindle shaped with indistinct border(syncytial)

### Medulloblastor



- It is one of the most common neoplasms of the <u>childhood</u>
- It is the highly malignant tumor of the cerebellum.
- Medulloblastoma are highly radiosensitive tumor of the CNS and more radiosensitive than
   Glioma
- The tumor which spread along the CSF pathway is Medulloblastoma
- This is the Tumor which is capable of metastasizing to extra-cranial site

### Ependymoma



- Gross appearance: circumscribed tumor with papillary architecture
- Microscopic:
  - ✓ Ependymal Rosettes: cells organized around the lumen
  - ✓ Perivascular pseudorosettes: cell organized around small vessels

Neuroanatomy, Neurophysiology & Neuropathology

# Cushing's



- Cushing triad for elevated ICP:
  - ✓ Bradycardia
  - ✓ Bradypnea
  - ✓ Hypertension
- Cushing reflex:
  - ✓ It is a physiological nervous system response to increased intracranial pressure (ICP) that result in Cushing triads of increased blood pressure, irregular breathing and bradycardia
  - ✓ It is usually seen in the terminal stage of acute head injury and may indicate imminent. brain herniation
- Cushing syndrome:
  - ✓ Increase in cortisol due to variety of causes
- · Cushing disease:
  - Cushing syndrome secondary to the pituitary tumor is called Cushing disease

### Hydrocephalus

Hydrocephalus is the excessive accumulation of CSF within the brain, and maybe caused either by increased CSF production, by reduced CSF absorption, or by the obstruction of the circulation

### Clinical features:

- Bulging eye----sunset eyes
- Dilated scalp vein
- Macewen sign, "Cracked pot"
- Brisk tendon reflexes "spasticity"
- Prominent occiput (dandy walker)
- Large tense anterior fontanelle
- Irritability and seizure

### Normal pressure hydrocephalus (NPH):

- NPH is a controversial entity, said to involve an intermittent rise in CSF pressure, particularly at night.
- . It is described in old age as being associated with a triad of gait apraxia, dementia and urinary incontinence
- Headache and other sign of raised intracranial pressure e.g. papilledema typical don't appear

# C H A P T E RLOWER LIME

### **Bones of Foot**

There are three groups of bones in the foot

- The seven tarsal bones, which form the skeletal framework for the ankle;
- Metatarsals (I to V), which are the bones of the metatarsus;
- The phalanges, which are the bones of the toes-each toe has three phalanges, except for the great toe, which has two.

### Tarsal bones

The tarsal bones are arranged in a proximal group and a distal group with an intermediate bone between the two groups on the medial side of the foot

### 1) Proximal group

The proximal group consists of two large bones, the talus (Latin for ankle) and the calcaneus (Latin for heel):

#### \* Talus bone

- No muscular attachment
- Form pillar of the medial arch
- Second largest tarsal bone

### Head of Talus

✓ Anterior articular surface is larger, oval and convex articulating with Navicular bone

✓ The Inferior surface has two facets medial and lateral for articulation with calcaneum.

#### Calcaneus

. It is the largest of the tarsal bones-posteriorly it forms the bony framework of the heel and anteriorly projects forward to articulate with one of the distal group of tarsal bones (cuboid) on the lateral side of the foot.

### 2) Intermediate tarsal bone

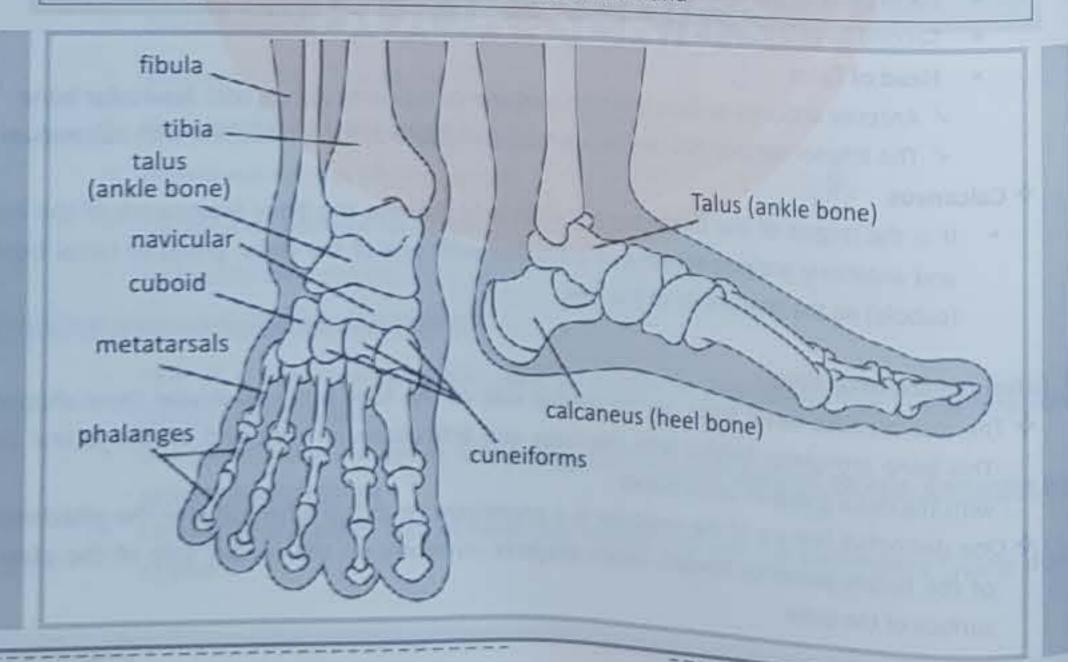
- . The intermediate tarsal bone on the medial side of the foot is the navicular (boat-shaped). This bone articulates behind with the talus and articulates in front and on the lateral side with the distal group of tarsal bones
- One distinctive feature of the navicular is a prominent rounded tuberosity for the attachment of the tibialis posterior tendon, which projects inferiorly on the medial side of the plantar surface of the bone.

From lateral to medial, the distal group of tarsal bones consists of:

- . The cuboid (Greek for cube), which articulates behind with the calcaneus and in front with the bases of the lateral two metatarsals-the tendon of the fibularis longus muscle lies in a prominent groove on the anterior plantar surface, which passes obliquely forward across the bone from lateral to medial;
- \* Three cuneiforms (Latin for wedge)-the lateral, intermediate, and medial cuneiform bones articulate behind with the navicular bone and in front with the bases of the medial three metatarsals.

### **Common Fractures and Dislocations**

- Commonly fracture bone in hand———Scaphoid bone
- Commonly dislocated bone in hand———Lunate bone
- Most common site of fracture of femur is -----neck
- Most common bone fracture in old age———femur
- After knee joint dislocation most important is the assessment of dorsalis Pedis artery
- Bunion is a bony bump that forms on the joint at the base of big toe
- Largest bone:
  - The Largest bone in hand------ Capitate bone
  - The Largest bone in foot------ Calcaneum bone
  - The Largest bone in body---
- Smallest bone:
  - ----Smallest bone of the hand Pisiform-----



### Chapter 8

### Lower Limb

### Joints of lower limb

### Ankle joint:

- The ankle joint is synovial in type and involves the talus of the foot and the tibia and fibula of the leg
- The ankle joint mainly allows hinge-like dorsiflexion and plantarflexion of the foot on the leg
- Dorsiflexion by: Tibialis anterior, PERONEUS tertius
- Planter flexion by: Peroneus longus, Peroneus Brevis, plantaris, soleus, Gastrocnemius

### Knee joint:

- The knee joint is the largest synovial joint in the body
- Basically the joint is a hinge joint that allows mainly flexion and extension
- There are two menisci, which are fibrocartilaginous C-shaped cartilages, in the knee joint, one medial (medial meniscus) and the other lateral (lateral meniscus). Both are attached at each end to facets in the intercondylar region of the tibial plateau.
- The medial meniscus is attached around its margin to the capsule of the joint and to the medial (tibial) collateral ligament whereas the lateral meniscus is unattached to the capsule. Therefore, the lateral meniscus is more mobile than the medial meniscus. The lateral (fibular) collateral ligament is separated from lateral meniscus by popliteus tendon.
- The joint between the femur and the tibia is synovial modified hinge joint, with some degree of Rotatory movement
- The Joint between the femur and Patella is a synovial plane gliding joint
- Fibula doesn't participate in the knee joint
- Structures inside the knee joint-----Intracapsular structure
  - √ Cruciate ligament
  - Popliteus muscle tendon and The two menisci

#### Patella

The patella (kneecap) is the largest sesamoid bone (a bone formed within the tendon of a muscle) in the body and is formed within the tendon of the quadriceps femoris muscle as it crosses anterior to the knee joint to insert on the tibia.

### Subtalar joint

- Inversion and Eversion occurs in Subtalar joint
- Inversion by: Tibialis anterior and Tibialis posterior, extensor hallucis longus and extensor digitorum longus (medial fibers)
- Eversion by: Peroneus longus, brevis and tertius, extensor digitorum longus (lateral fibers)

### Arch of foot

### Medial arch

- Pillar of the medial arch is formed by talus bone
- Form by all tarsal bone except----cuboid bone and lateral tarsal bone
- The Most important ligament in medial arch---plantar calcaneonavicular ligament

### Lateral arch

Formed by cuboid bone, lateral two metatarsal and calcaneum

### Transverse arch

Formed by cuboid bone, three cuneiform bones and bases of metatarsal bones

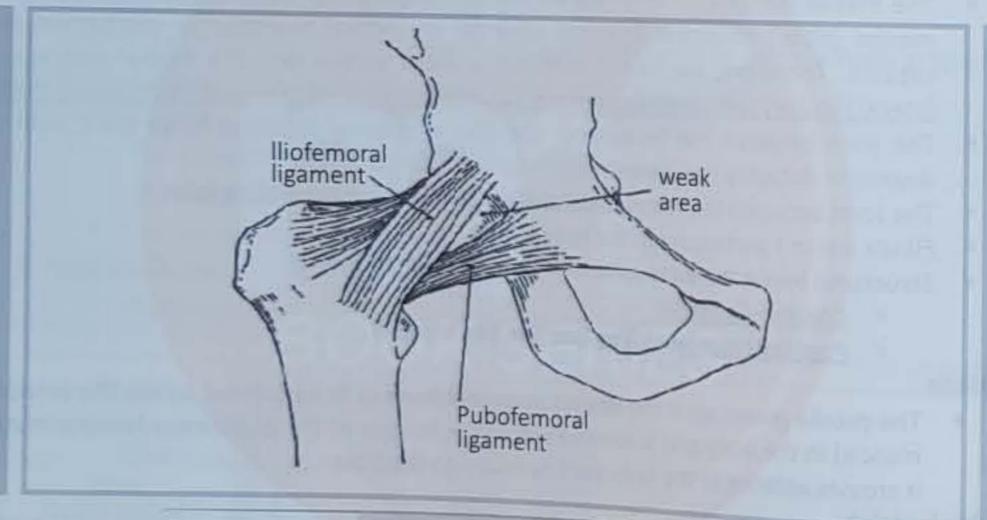
Lower Limb

### Ligament of Lower Limb

### Hip joint ligament

The hip joint is a ball and socket joint, stabilized by the static and dynamic stabilizer. The Static stabilizers includes the capsule, ligament (Given below in detail), and labrum. Dynamic stabilizers consist of the muscle acting across the joint

- Iliofemoral ligament
  - Strongest ligament and most important ligament of hip joint, Y shaped
  - Prevent hyperextension and lateral rotation
- Ischiofemoral ligament
  - Spiral shape
  - Weakest
  - Prevent medial rotation
- Pubofemoral ligament
  - Triangular in shape
  - Prevent extensive abduction and lateral rotation



### **KNEE JOINT**

- Anterior cruciate ligament(ACL)
  - It is the most common knee ligament injuries seen in all form of sports
  - It is attached to the Anterior intercondylar area of TIBIA
  - it prevents ANTERIOR dislocation of TIBIA on the femur and POSTERIOR dislocation of
  - Positive anterior drawer sign-----ACL tear
- Posterior cruciate ligament
  - It is attached to the posterior intercondylar area of the tibia
  - It is attached to the post-It prevents ANTERIOR dislocation of FEMUR on the tibia and POSTERIOR dislocation of

### Ligamentum patellae

Chapter 8

It is the continuation of the tendon of quadriceps femoris.

### Oblique Popliteal ligament

It is a tendinous expansion of semimembranosus muscle. It strengthens the posterior aspect of the capsule

### Collateral ligament:

- Medial collateral ligament (MCL):
  - ✓ The medial collateral ligament a medial stabilizer of the knee and is most. commonly injured by direct blow to the lateral aspect (outside) of the knee or by the patient planting the foot and then colliding with another athlete
- Lateral collateral ligament (LCL):
  - ✓ Injury to the lateral collateral ligament is less common but more disabling. It occurs via hyperextension with varus stress or from a direct blow or rotation
  - LCL Damaged by blow to medial side—inside (Varus force )

### **Foot Ligament**

### Deltoid ligament:

- It is also called medial ligament
- The medial ligament is large, strong, and triangular in shape
- injury occurs due to Excessive Eversion of foot

### Lateral ligament:

- Weaker than medial ligament and consist of three band
  - ✓ Anterior talofibular ligament
  - ✓ Posterior talofibular ligament
  - ✓ Calcaneofibular ligament

#### Clinical Pearls:

- ✓ The Most common type of injury is inversion because of this weak lateral ligament
- Most common ligament injury is lateral ligament and most common among subtype ligament injury is the anterior talofibular ligament
- ✓ Twisting inversion accounts for the common strain to anterior talofibular part of the lateral ligament

### Plantaris tendon rupture:

- Patient can stand on foot but hurt (painful)
- Patient will be present like, a 25 years old sprinter or athlete during running had injury to his ankle, he can stand on his toes but with severe pain. The next day he noticed visible ecchymosis around ankle joint

### Achilles tendon rupture:

- Achilles tendon rupture is when Achilles tendon, at the back of the ankle breaks, symptoms include sudden onset of sharp pain in the heel. A snapping sound may be heard as the tendon break and walking become difficult
- Patient can't stand on the toes

Lower Limb

# Muscle of Lower Limb

# Thigh and Gluteal Region

### Gluteal Region

- . Gluteus maximus: Cause extension of both joints, it is also assisted by tensor fascia lata, the largest muscle responsible for the prominence of the buttock.
- The gluteus maximus, gluteus medius and gluteus minimus: The three muscles originate from the ilium and sacrum and insert on the femur.

### Thigh

- . The Anterior compartment of thigh contains muscles that mainly extend the leg at the knee joint
- . The Posterior compartment of thigh contains muscles that mainly extend the thigh at the him joint and flex the leg at the knee joint;
- The Medial compartment of the thigh consists of muscles that mainly adduct the thigh at the hip joint.

### 1) Anterior compartment

- All supplied by femoral nerve except psoas which is supplied by lumbar plexus
- Flexion in hip and extension in the knee
- . The Muscle which FLEX the THIGH and EXTEND the LEG is Rectus femoris
- Muscles:
  - Sartorius muscle:
    - Flexor of both hip and knee joint
    - ✓ Originated from the anterior superior iliac spine and insert on proximal tibia, medial to the tibial tuberosity
    - ✓ Fracture of the anterior superior iliac spine will cause damage to Sartorius muscle
  - Four large quadriceps femoris muscles (rectus femoris, vastus lateralis, vastus medialis, and vastus intermedius)
  - The rectus femoris muscle crosses both the hip and the knee joints.
  - Vastus lateralis originates from the femur and contribute directly to the stability of the knee joint.
  - The lowest fibers of the vastus medialis, inserted into the border of the bone, hold the patella medially when the quadriceps contract. These fibers of vastus medialis are indispensible to the stability of the patella. (Reference: RJ LAST's Anatomy 12th edition P.120)
  - @ Iliacus muscle
  - Psoas muscle
    - ✓ Absent in 40% of cases
    - ✓ Supplied by lumbar plexus
    - ✓ Form medial Arcuate ligament
    - ✓ Originate from all lumbar vertebra (L1-L5) and insert on lesser trochanters of
    - ✓ Psoas abscess: Painless swelling in inguinal region
      - Clinical features: Classical triad: fever, back pain and limp.
      - O Position of comfort: supine with knee moderately flexed, hip mildly

### 2) Medial compartment

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- Muscle of medial compartment are Collectively known as hip adductor
- Supplied by Obturator nerve
- Muscles
  - Gracilis,
  - · Obturator externus,
  - · Adductor brevis,
  - · Adductor longus and
  - Adductor magnus:
    - ✓ Adductor magnus is the largest and deepest of the muscles in the medial compartment of thigh
    - ✓ Two portions:
      - Adductor portion-----supplied by Obturator nerve
      - Hamstrung portion----supplied by the tibial nerve

### 3) Posterior compartment

- The Posterior compartment of thigh contains three large muscles termed the 'hamstrings'.
- Function: Extends hip, flexes knee---important for walking/running
- Muscles
  - √ Biceps femoris: two head
    - Short head------Flexes knee--Supplied by common peroneal nerve
    - o Long head-----Extend hip---Supplied by tibial nerve
  - ✓ Semitendinosus and Semimembranosus
    - Origin: ischial tuberosity (this is also the origin of long head of biceps femoris)
    - o Action: Extends hip, flexes knee



### Anterior compartment

- There are four muscles in the anterior compartment of the leg: tibialis anterior, extensor hallucis longus, extensor digitorum longus, and fibularis tertius.
- Collectively they dorsiflex the foot at the ankle joint, extend the toes, and invert the foot.
- All are innervated by the deep fibular nerve, which is a branch of the common fibular nerve.
- The compartment most commonly affected in a lower leg compartment syndrome is the anterior compartment of the leg. Numbness in the web-space between the first and 2<sup>nd</sup> toes is diagnostic due to compression of the deep peroneal nerve.

### **Posterior Compartment**

- Muscles in the posterior (flexor) compartment of leg are organized into two groups, superficial and deep, separated by a layer of deep fascia.
- Generally, the muscles mainly plantarflex and invert the foot and flex the toes.
- All are innervated by the tibial nerve
- The gastrocnemius muscle is the most superficial of the muscles in the posterior compartment and is one of the largest muscles in the leg
- Superficial group:
  - ✓ The superficial group of muscles in the posterior compartment of leg comprises three muscles: Gastrocnemius, Plantaris and Soleus

- ✓ As a unit, these muscles are large and powerful because they propel the body forward to the planted foot during walking and can elevate the body upwards onto the toes when
- ✓ All of which insert onto the heel (calcaneus) of the foot and plantarflex the foot at the ankle joint
- Deep group
  - ✓ There are four muscles in the deep posterior compartment of leg-popliteus, flexor hallure longus, flexor digitorum longus, and tibialis posterior.
  - ✓ The popliteus muscle acts on the knee whereas the other three muscles act mainly on the foot.

### **Lateral Compartment**

- There are two muscles in the lateral compartment of leg-fibularis longus and fibularis brevis (also known as peroneal longus and brevis).
- Both evert the foot (turn the sole outwards) and are innervated by the superficial fibular nerva which is a branch of the common fibular nerve.



### Muscles of Anterior Abdominal Wall

From superficial to deep

- Skin
- Superficial fascia
- Muscles (The external oblique muscle is the outermost muscle, whose fibers run inferomedially Right beneath it sits the internal oblique muscle whose fibers run superomedially. The most profound lateral muscle is the transversus abdominis which consists of horizontal fibers. The transverse fascia is located below the transversus abdominis. )
- Transversalis fascia
- Extraperitoneal fat (extraperitoneal fascia)

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NAME AND ADDRESS OF THE OWNER, WHEN PERSON NAMED IN

Peritoneum

### External Oblique

- The external oblique muscle is the largest and the most superficial (outermost) of the three flat muscles of the lateral anterior abdomen. Fiber passes downward and forward
- . The Upper end of external oblique-----Serratus anterior
- --- latissimus dorsi The Lower end of external oblique----
- -External oblique aponeurosis External oblique form-
- Spermatic cord carries this as external spermatic fascia—which forms external cover of spermatic cord
- Defect in external oblique -

Superficial inguinal ring

The Lower end of aponeurosis folded back on itself and form-----Inguinal ligament From medial end of inguinal ligament extend-

-----Lacunar ligament

The Pectineal ligament is an extension of the lacunar ligament

### Internal Oblique

- Originating from the thoracolumbar fascia, iliac crest and iliopectineal arch, the internal oblique muscle inserts cranially at the lower costal cartilages and ventrally at the linea Alba.
- Spermatic cord carries some fibers from internal oblique and called cremasteric fascia, a term

Lower Limb Chapter 8

### Transverse Abdominis Muscle

- Joins internal oblique and forms conjoint tendon
- Joins fascia iliaca and forms the femoral sheath
- Forms the transversalis fascia
- Forms deep inguinal ring and internal spermatic fascia
- No attachments with the lumbar vertebra

### **Rectus Abdominis Muscle**

- The rectus abdominis muscles are a pair of long, straight muscles which run vertically on either side of the anterior abdominal wall. They are separated by the linea Alba.
- Each muscle consists of a string of four fleshy muscular bodies connected by three narrow bands of tendon known as tendinous intersections. The shape of these segments is often visible through the superficial fascia and skin in those with low body fat, resulting in a 'six-pack' shape.

### Pyramidalis Muscle

- Contained in the rectus sheath
- Supplied by subcostal nerve
- Originate from pubic Symphysis and insert on the linea alba
- Paired muscle
- Often absent
- Lies in front of the lower part of the rectus abdominis

### Nerve supply of external oblique, internal oblique and transverses abdominis Muscle

Present between the internal oblique and transversalis muscle

- Lower six thoracic nerve
- Iliohypogastric nerve
- Ilioinguinal nerve

### **Rectus Sheath**

- The rectus sheath is a long fibrous sheath that encloses the rectus abdominis muscle and pyramidalis muscle (if present) and contains the anterior rami of the lower six thoracic nerves and the superior and inferior epigastric vessels and lymph vessels. It is formed mainly by the aponeuroses of the three lateral abdominal muscles
- It should be noted that where the aponeuroses forming the posterior wall pass in front of the rectus at the level of the anterior superior iliac spine, the posterior wall has a free, curved lower border called the arcuate line. At this site, the inferior epigastric vessels enter the rectus sheath and pass upwards to anastomose with the superior epigastric vessels.
- The rectus sheath is separated from its fellow on the opposite side by a fibrous band called the linea alba
- The posterior wall of the rectus sheath is not attached to the rectus abdominis muscle. The anterior wall is firmly attached to it by the muscle's tendinous intersections
- Rectus sheath hematoma: Hematoma of the rectus sheath is uncommon but important, since it is often overlooked. It occurs most often on the right side below the level of the umbilicus. The source of the bleeding is the inferior epigastric vein or, more rarely, the inferior epigastric artery. An acutely tender mass confined to one rectus sheath is diagnostic

Lower Limb

# Inguinal Ring, Canal, Femoral Triangle and Adductor canal

# Contents of Greater and Lesser Sciatic Foramen

S.No	Greater Sciatic foramen	Lesser Sciatic foramen
	Pudendal nerve	Pudendal nerve
2.	Posterior cutaneous nerve of the thigh	Tendon of Obturator internus
3.	Piriformis muscle	Internal Pudendal vessels
4.	Superior and inferior Gluteal vessel	Nerve to Obturator internus
5.	Superior and inferior Gluteal nerve	
6.	Nerve to Obturator internus	
7.	Nerve to quadratus femoris	
8.	Internal Pudendal vessels	

### Inguinal Canal

### **Boundaries: MALT**

- Superior wall (roof)—2-Muscles
  - ✓ Internal oblique Muscle and transverse abdominis Muscle
- Anterior wall—2-Aponeurosis: -
  - ✓ Aponeurosis of internal oblique and external oblique
- · Lower wall (Floor): 2 ligament
  - ✓ lower wall: inguinal Ligament and lacunar Ligament
- Posterior wall—2Ts
  - ✓ Transversalis fascia and Conjoined Tendon

### Structures passing through the canal: Contents

- . Spermatic cord in the male and the round ligament of the uterus in the female
- Ilioinguinal nerve

### Structures of the spermatic cord:

- Testicular artery, testicular vein (Pampiniform plexus) and Testicular lymph vessels
- Vas deferens
- Autonomic nerves
- Remains of Processus vaginalis
- Genital branch of the Genitofemoral nerve, which supply cremaster muscle

### Femoral Canal

 The femoral canal is an anatomical compartment, located in the anterior thigh. It is the smallest and most medial part of the femoral sheath. It is approximately 1.3cm long.

It can be thought of as a rectangular shaped compartment.

### It has four borders and an opening:

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Chapter 8

Medial border	Lacunar ligament	
Lateral border	Femoral vein	
Anterior border	Inguinal ligament	
Posterior border	Pectineal ligament, superior ramus of the pubic bone, and the pectineus muscle	

The opening to the femoral canal is located at its superior border, known as the femoral ring. The femoral ring is closed by a connective tissue layer - the femoral septum. This septum is pierced by the lymphatic vessels exiting the canal.

#### Contents

- ✓ Lymphatic vessels draining the deep inguinal lymph node
- Deep lymph node the lacunar node
- Empty space
- ✓ Loose connective tissue

#### Physiological significance:

✓ The empty space allows distension of the adjacent femoral vein, so it can cope with increased venous return, or increased intra-abdominal pressure.

### Pathological significances:

- ✓ As a potential space, it is the site of femoral hernia. The relatively tight neck places these at high risk of strangulation
- ✓ The femoral vein lies immediate lateral to the femoral canal. Careful attention to this structure is essential in repair of femoral hernia.

### **Femoral Ring**

The femoral ring is the base of the femoral canal. It is directed upward and is oval in form, its long diameter being directed transversely and measuring about 1.25 cm. Part of the intestine can sometimes pass through the femoral ring into the femoral canal causing a femoral hernia.

#### Boundaries:

Anterior	Inguinal ligament	
Posterior	Superior ramus of pubis	
Medial	Lacunar ligament	
Lateral	Femoral vein	

#### Contents:

Cloquet's node and lymphatics

Lower Limb

. The femoral triangle is a wedge-shaped depression formed by muscles in the upper thigh at the junction between the anterior abdominal wall and the lower limb

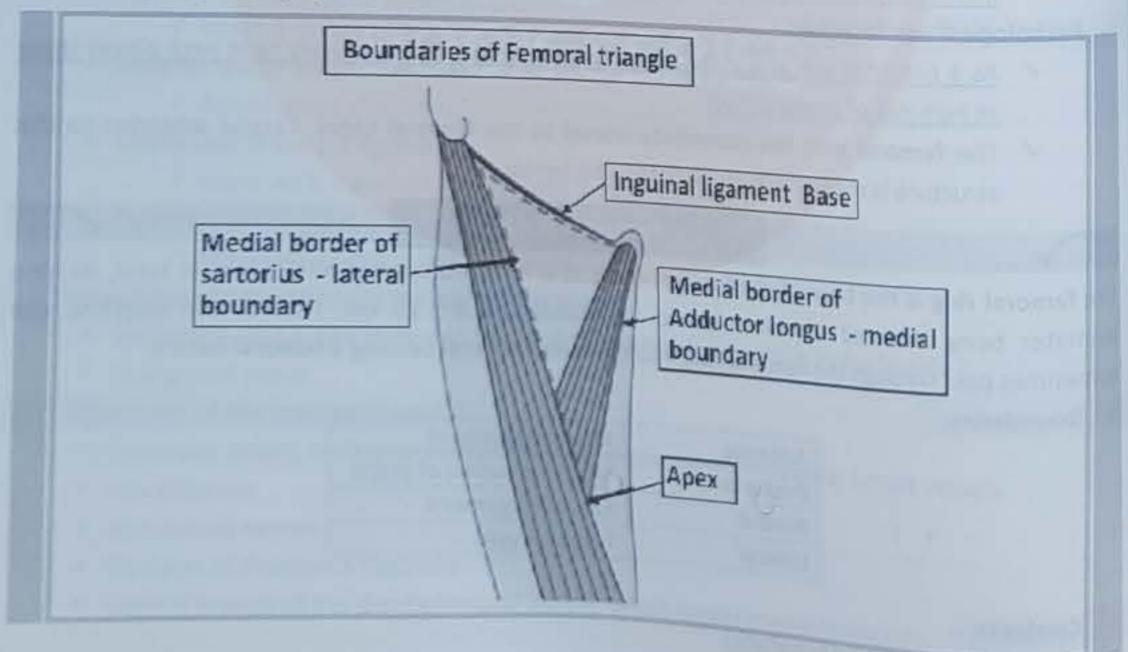
Inquinal ligament is common structure of femoral and Hesselbach's triangle. It Forms the superior border/base in femoral triangle and forms inferior border/base in Hesselbach's triangle

#### Boundaries

Superiorly/base	The inguinal ligament	
Laterally	The Sartorius anterior	
Medially	The adductor longus muscle	
Apex	The apex of the femoral triangle points inferiorly and continuous with an adductor canal	

### Contents: NAVEL - from lateral to medial

- The Terminal part of femoral Nerve
- The femoral sheath
- The femoral Artery and its branches
- The femoral Vein and its tributaries
- Empty space (this is important as it allows the veins and lymph vessels to distend so they can cope with different level of flow)
- Deep inguinal Lymph nodes



### Deep and Superficial Inguinal Ring

The two openings to the inguinal canal are known as rings

### Deep (internal) ring:

@:0:0:e

Chapter 8

- It is found above the midpoint of the inguinal ligament, which is bounded, above and laterally by arched lower margin of fascia transversalis, below and medially, by the inferior epigastric vessels
- The ring is created by transversalis fascia, which invaginates to form the covering of the content of the inguinal canal

### Superficial inguinal ring:

- It marks the end of the inguinal canal and lies just superior to the pubic tubercle
- It is a triangle-shaped opening formed by the invagination of the external oblique
- This opening contains intercrural fibers, which runs perpendicular to the aponeurosis of the external oblique and prevent the ring from widening
- Ilioinguinal nerve: it only travels through part of the inguinal canal existing via the superficial inguinal ring. It does not pass through the deep inguinal ring

### **Femoral Sheath**

- Formed by the extension of two layer of the fascia of the abdomen, anterior wall of the sheath is formed by fascia transversalis and posterior wall by fascia iliaca.
- The femoral canal (the opening is called the femoral ring) is the most medial portion of the femoral sheath.
- \* Lateral to the femoral sheath is a muscular lacuna, bordered by the inguinal ligament, innominate bones anterior edge, and iliopectineal arch. The femoral nerve and iliopsoas muscle pass through this muscular lacuna. (Femoral Nerve----Lateral, femoral sheath medial)
- Contents: AVEL--- From lateral to medial----Compare this with femoral triangle contents
  - Lateral compartment: Femoral Artery, this is the most lateral structure
  - Intermediate compartment Femoral Vein----
  - Medial compartment, the medial and smallest compartment is called the femoral canal
  - Empty space
  - · Lymph node

### Hesselbach's Triangle

### Boundaries:

- ✓ Medially-----Lateral border of the rectus muscle
- ✓ Laterally-----Inferior epigastric artery
- ✓ Inferiorly/base-----Inguinal ligament

### Clinical Significance:

- ✓ Direct inguinal hernia occurs through Hesselbach's triangle
- ✓ Indirect inguinal hernia passes lateral to the inferior epigastric vessels into the deep inguinal ring, and are therefore lateral to Hesselbach's triangle

### Adductor Canal or Hunter Canal

### **Boundaries**

- -Sartorius Anteromedial-
- -vastus medialis Lateral-----
- -- adductor longus and magnus Posterior-----

#### Content

- The Terminal part of femoral artery and vein
- The Terminal part of Obturator nerve
- Saphenous nerve and nerve to the vastus medialis



### **Saphenous Opening**

- Saphenous opening (saphenous hiatus, fossa ovalis) is an oval opening in the upper mid part of fascia lata of the thigh
- It lies 3-4-cm below and lateral to the pubic tubercle and is about 3cm long and 1.5cm wide
- Structures: just inferolateral to the pubic tubercle the fascia extends downwards forming an arched (falciform) margin of the lateral boundary of the opening. It is covered by a thin perforated part of the superficial fascia called the fascia cribrosa which is pieced by the great saphenous opening, the three superficial branches of the femoral artery and lymphatics
- The fasica cribrosa, which is pierced by the structures passing through the opening close the aperture and must be removed to expose it
- It transmits:
  - ✓ Great saphenous vein and other smaller vessels including.
    - Superficial epigastric artery
    - Superficial external pudendal artery
    - o Femoral branch of the Genitofemoral nerve



### **Popliteal Fossa**

- The popliteal fossa is an important area of transition between the thigh and leg and is the major route by which structures pass from one region to the other.
- The popliteal fossa is a diamond-shaped space behind the knee joint formed between muscles in
- Boundaries:
  - ✓ Upper lateral boundary:
    - o Biceps femoris muscle
  - ✓ Upper medial boundary:
    - Semitendinosus and semimembranosus muscles
  - ✓ Two lower boundaries:
    - The head of gastrocnemius muscle
  - The floor of the fossa is formed by the capsule of the knee joint and adjacent surfaces of

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the femur and tibia, and by the popliteus muscle;

✓ The roof is formed by deep fascia, which is continuous above with the fascia lata of the thigh and below with deep fascia of the leg.

### Contents: From superficial to deep

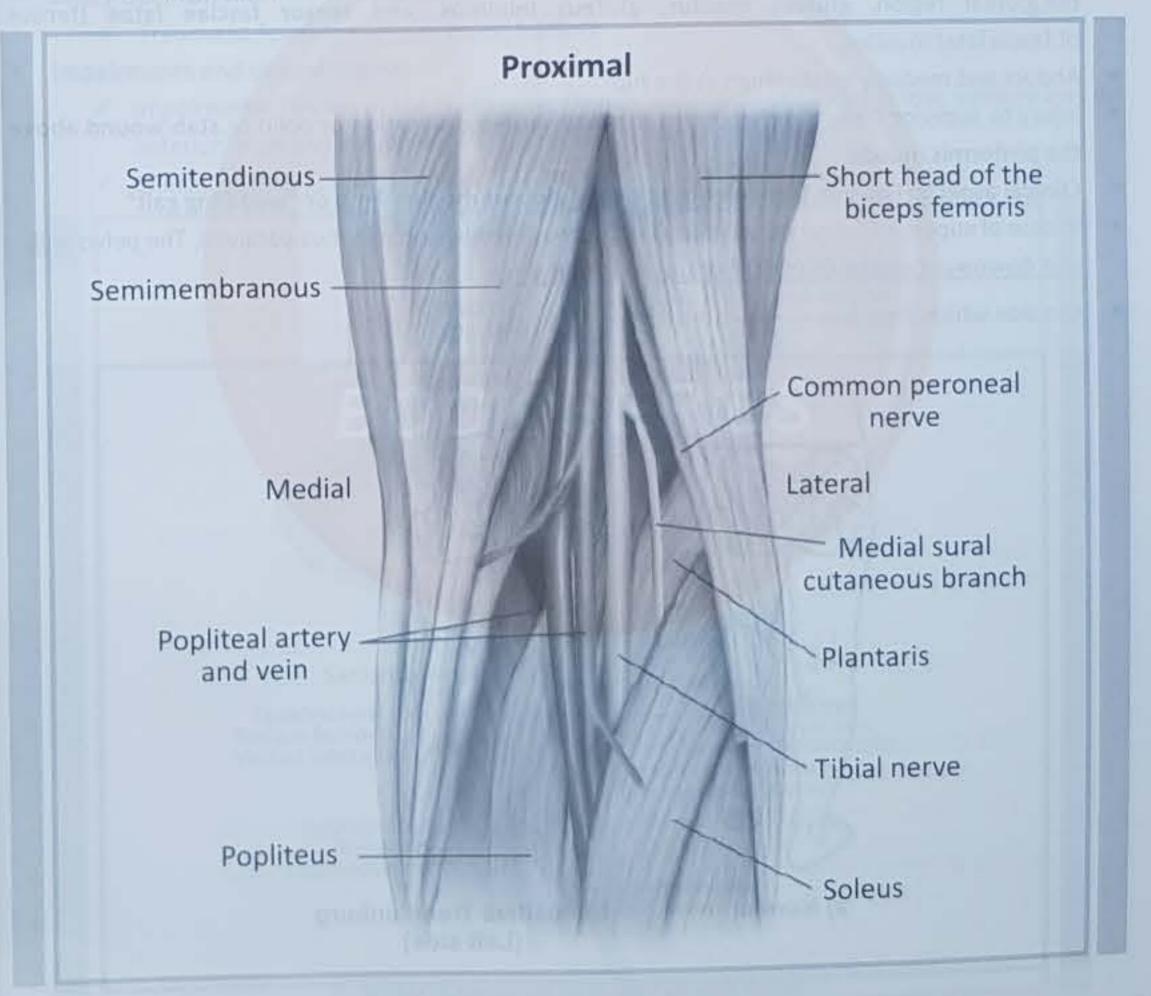
✓ Tibial nerve

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- ✓ The popliteal vein
- The popliteal artery
- ✓ Common peroneal nerve-----which is medial to bicep femoris tendon

### Clinical notes

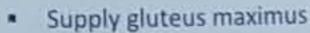
✓ The popliteal artery is the deepest of the neurovascular structures in the popliteal fossa. and is therefore difficult to palpate; however, a pulse can usually be detected by deep palpation medial to the midline.



### Chapter 8

# **Nerves of Lower Limb**

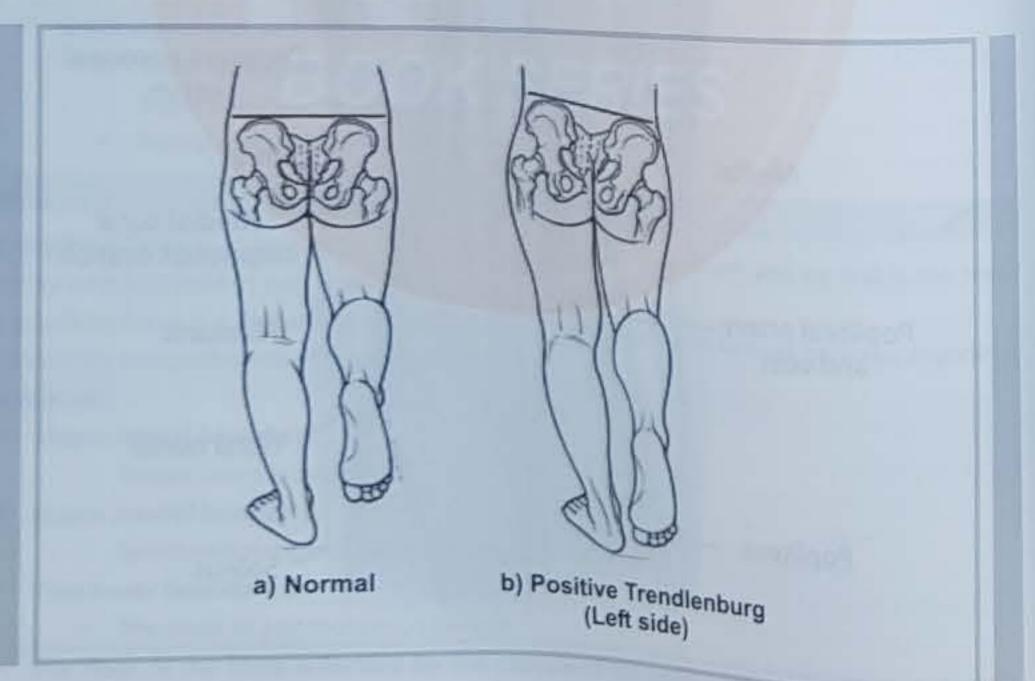
### Inferior Gluteal Nerve



- Main function is the extension of thigh and leg
- Injury occurs in posterior dislocation of the hip
- Clinical aspect: Patient will be unable to jump, climb stairs and will be unable to stand from sitting position, patient will lean the body trunk backward at the heal strike

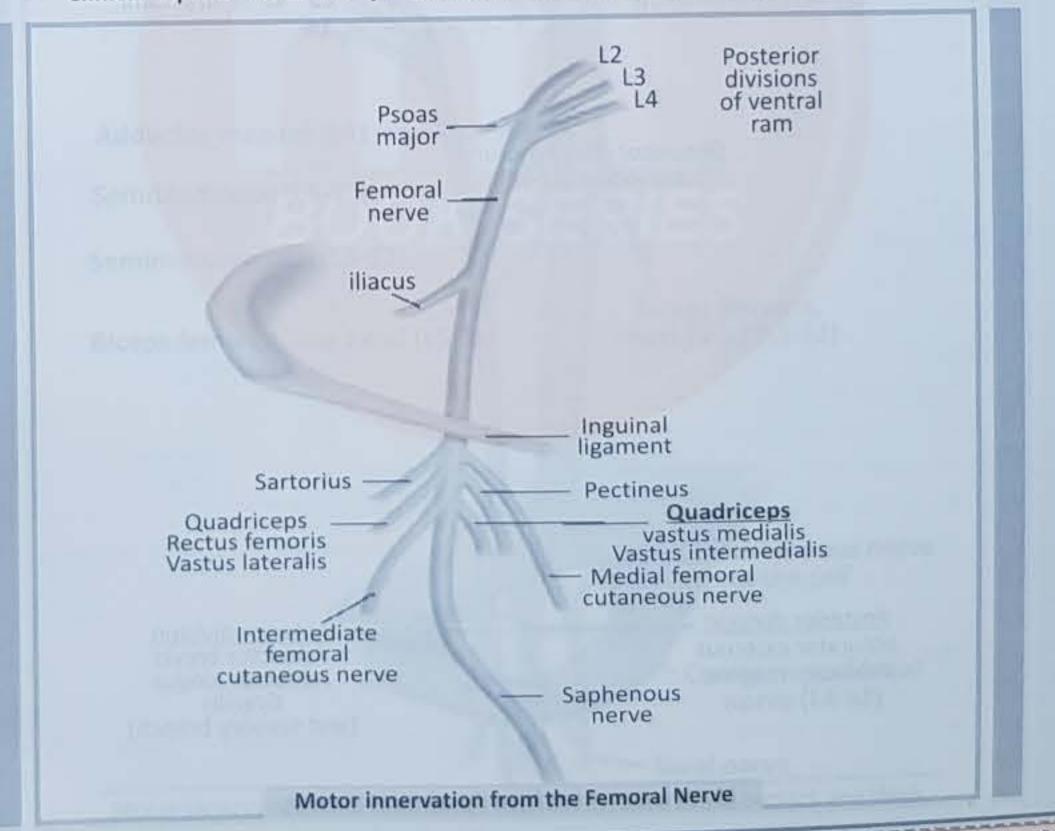
### **Superior Gluteal Nerve**

- The superior gluteal nerve, created by divisions via the dorsal branches of L4 to SI, exits the pelvicavity via the greater sciatic foramen superior to the piriformis muscle and supplies muscles the gluteal region, gluteus medius, gluteus minimus, and tensor fasciae latae (tensor fascia lata) muscles.
- Abduct and medially rotate thigh at the hip
- Injury to superior Gluteal nerve occurs in posterior hip dislocation or polio or stab wound about
  the piriformis muscle
- Clinical aspects: Positive Trendelenburg's sign, gluteus medius limp or "waddling gait"
- In case of superior Gluteal nerve injury i.e. Gluteus medius and minimus paralysis, The pelvis will sink downward on the OPPOSITE or unsupported side
- The side which sinks is——normal



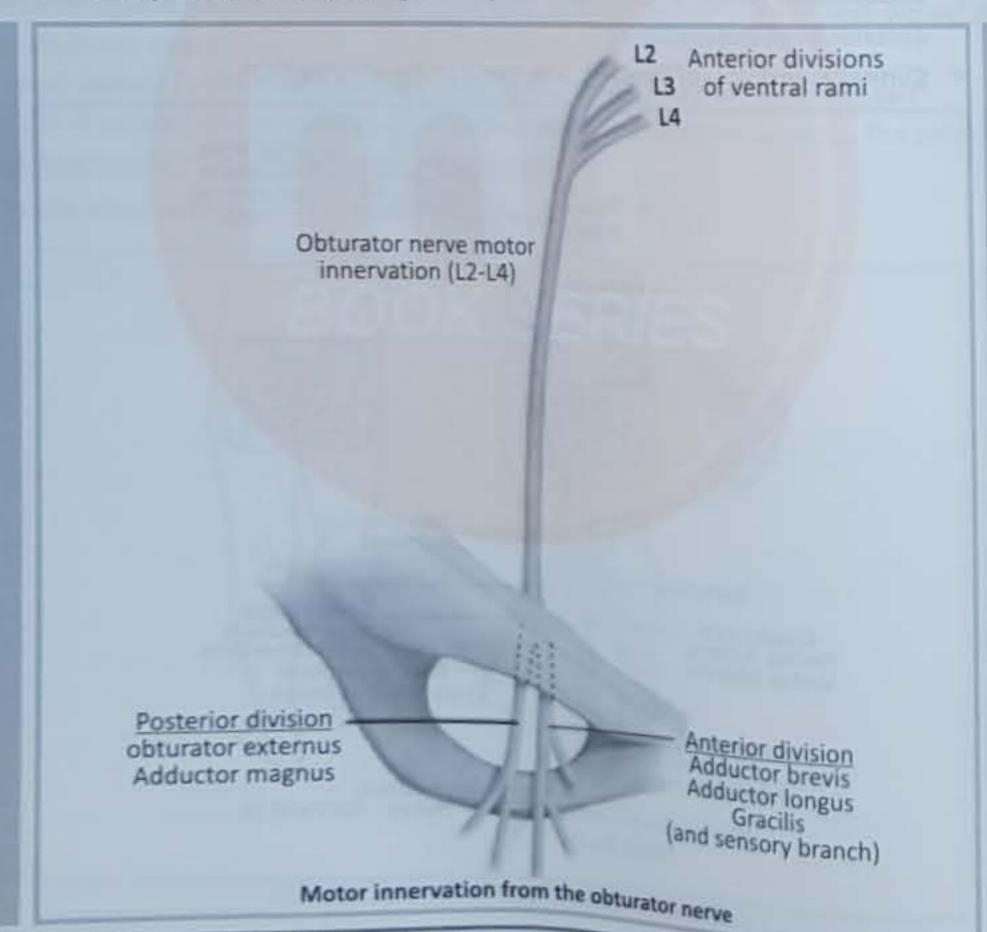
### **Femoral Nerve**

- The femoral nerve carries contributions from the anterior rami of L2 to L4 and leaves the abdomen by passing through the gap between the inguinal ligament and the superior margin of the pelvis to enter the femoral triangle on the anteromedial aspect of the thigh. Branches
  - ✓ Anterior cutaneous branches, which penetrate deep fascia to supply skin on the front of the thigh and knee
  - ✓ Numerous motor nerves, which supply the quadriceps femoris muscles (rectus femoris, vastus lateralis, vastus intermedius, and vastus medialis muscles) and the Sartorius muscle.
  - ✓ One long cutaneous nerve,
  - ✓ The saphenous nerve, which the terminal branch of femoral nerve and supplies skin as
    far distally as the medial side of the foot---Medial side of knee, leg and foot
- Injury description:
  - ✓ Trauma to femoral triangle, pelvic fracture
- Impairments and clinical aspect:
  - ✓ Impairment: Flexion of the thigh is weakened, extension of the leg is lost, sensory loss on anterior thigh and medial leg
  - ✓ Clinical aspect: loss of knee jerk, anesthesia on the anterior thigh



# Obturator Nerve: L2, L3, L4

- The obturator nerve (L2 to L4) is a branch of the lumbar plexus.
- It passes inferiorly along the posterior abdominal wall within the psoas muscle, emerges from a medial surface of the psoas, passes posteriorly to the common iliac artery and medially to s internal artery at the pelvic inlet, and then courses along the lateral pelvic wall. It leaves the pelvic cavity by traveling through the obturator canal
- Supplies medial/adductor compartment of thigh
- The obturator nerve is closely related to the bladder
- Injury description :
  - ✓ Anterior dislocation of hip joint
  - ✓ Injury Mostly 2cm below and lateral to the pubic tubercle
  - ✓ Radical retropubic prostatectomy
- Impairments:
  - ✓ Adduction of thigh Is lost
  - Sensory loss on the medial thigh

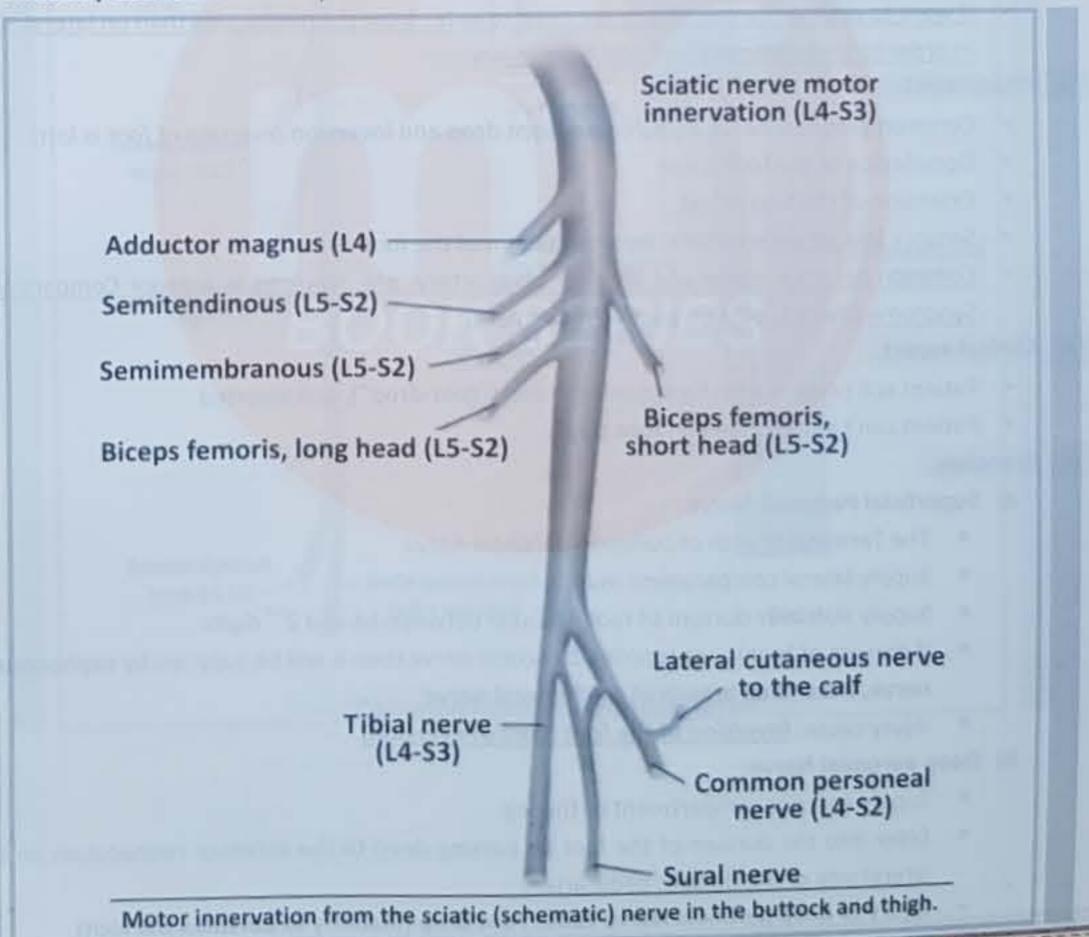


### Sciatic Nerve --- L4, L5, S1, S2, S3

The sciatic nerve is the largest nerve of the body

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- · Forms on the anterior surface of the piriformis muscle and leave the pelvic cavity through the greater sciatic foramen inferior to the piriformis
- Passes through the Gluteal region into the thigh, where it divides into its two major branches,
- The common fibular nerve (common peroneal nerve) and the tibial nerve
- · Posterior divisions of L4 to S2 are carried in the common fibular part of the nerve and the anterior divisions of L4 to S3 are carried in the tibial part.
- · Clinical Points: The greater thickness of the gluteus maximus muscle makes it ideal for intramuscular injection. To avoid injury to the underlying sciatic nerve, the injection should be given in the upper outer quadrant of the buttock (Reference: SNELL 8th edition P.565, RJ LAST's Anatomy 12th edition P.127)



Lower Limb

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- Smaller, Terminal branch of the sciatic nerve
- Easily palpable medial to bicep tendon
- Supplies all muscles of anterior and lateral compartments of leg
- Supplies short head of bicep muscle in the posterior compartment of thigh
- Extensor digitorum brevis in the foot (also contributes to the supply of the first dorse interosseous muscle)
- Sensory or cutaneous function: Skin on the anterolateral surface of the leg and dorsal surface of the foot
- Use for PED----Peroneal---for Eversion and Dorsiflexion
- Divide into superficial and deep peroneal nerve

#### Injury description:

- ✓ Blow to lateral aspects of leg
- ✓ Fracture of neck of the fibula
- If want to get the marrow biopsy we need to enter from the medial side than on lateral side in order to save common peroneal from injury

#### Impairment:

- Common peroneal nerve injury cause Foot drop and inversion (eversion of foot is lost)
- Dorsiflexion of the foot is lost
- Extension of the toes is lost
- Sensory loss on anterolateral leg and dorsum of the foot
- Common peroneal nerve and anterior tibial artery are involved in anterior Compartment Syndrome (there is pain on passive movement)

### Clinical aspect:

- Patient will present with foot plantar flexed ("foot-drop"), and inverted
- ✓ Patient can't stand on heels "foot slap"

#### Branches:

#### a) Superficial Peroneal Nerve

- . The Terminal branch of common peroneal nerve
- Supply lateral compartment muscle
- Supply skin over dorsum of foot, the skin between 1st and 2<sup>nd</sup> digits
- If dorsum of foot is not supplied by sciatic nerve then it will be supplied by saphenous nerve, a terminal branch of the femoral nerve
- injury cause: Inversion of the foot (Loss of eversion)

### b) Deep peroneal Nerve:

- Supply anterior compartment of the leg
- Supply arried
   Enter into the dorsum of the foot by passing deep to the extensor retinaculum on the
- Injury to deep peroneal Nerve cause Foot drop (inability to dorsiflex the foot)

Proximal Common peroneal Common Fibular peroneal head nerve Deep peroneal -Tibia -Tibialis anterior (L4-51) Medial Superficial peroneal Lateral nerve Peroneus longus Extensor digitorum longus (L5,51) Superficial Peroneal nerve Deep peroneal nerve Extensor hallucis longus (L5)

Medial terminal branch

to first web space

Common Peroneal/Fibular Nerve

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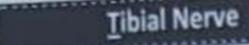
Distal

Extensor digitorum

brevis (L5, 51)

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Lower Limb



- This is the large terminal branch of sciatic that arises in the lower third of the thigh and enterpretarior compartment of thigh
- Supplies All muscles in the posterior or hamstring compartment of the thigh(including the hamstring part of the adductor magnus) except for the short head of the biceps which is supplied by the common peroneal nerve)
- · Supplies All muscles in the posterior compartment of the leg
- Supplies All muscles in the sole of the foot
- Sensory (cutaneous) function: Skin on posterolateral and medial surfaces of foot and sole of the foot (the plantar aspect of foot)
- · Function: TIP----Tibial nerve cause Inversion and Plantarflexion

#### Clinical notes:

- ✓ Commonly injured in knee trauma
- ✓ Injury to tibial Nerve cause Dorsiflexion and eversion of the foot at Subtalar and transtarsal joints (loss of inversion)
- ✓ <u>Tarsal tunnel syndrome</u>: it is Due to entrapment of Tibial Nerve while passing deep to flexor retinaculum in between medial malleolus and calcaneum

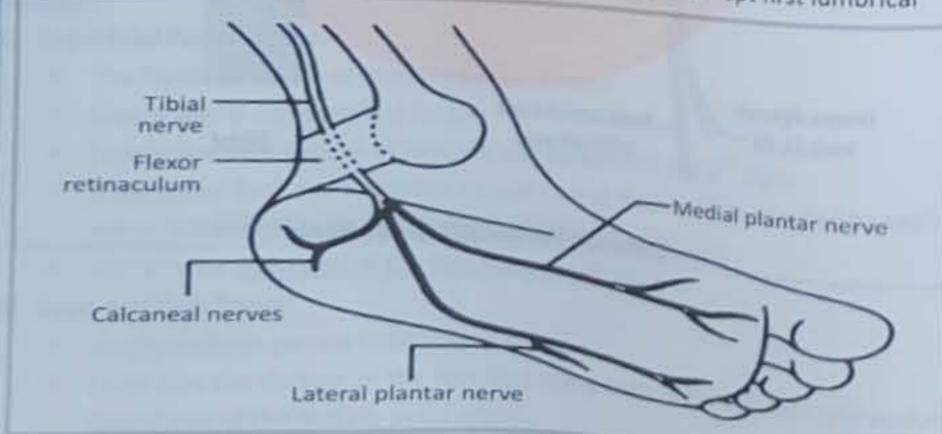
#### Divide into

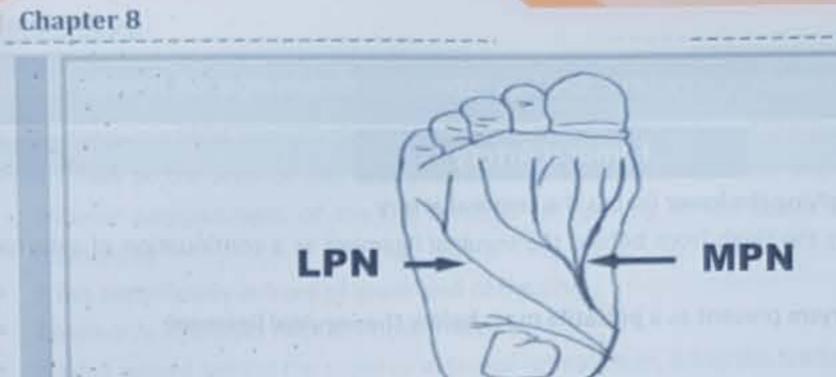
### a) Medial plantar nerve (MPN)

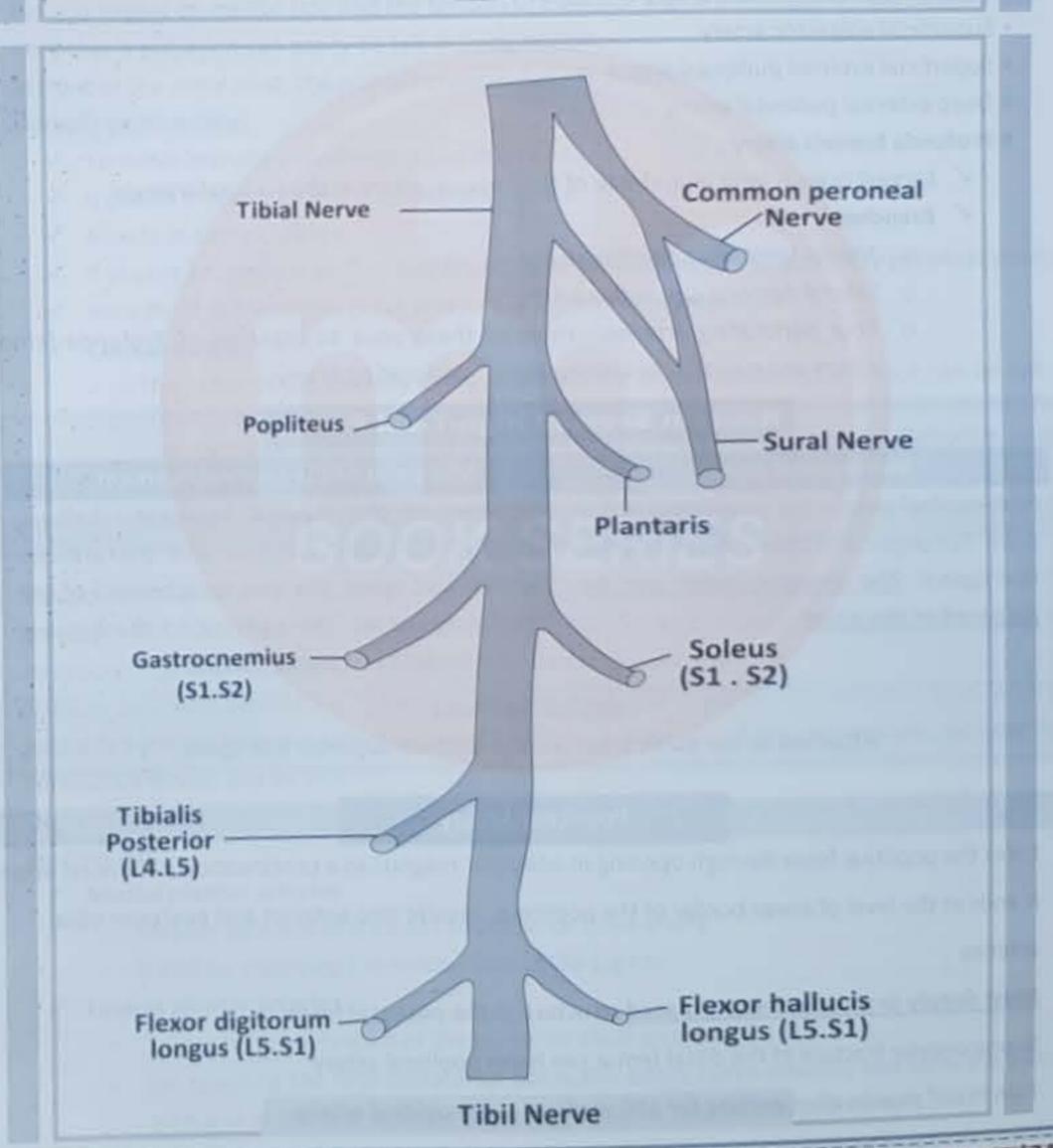
- · Arise beneath flexor retinaculum
- Like median nerve, it supplies LOAF muscle
- Supply medial 3 and half toes

### b) Lateral plantar nerve (LPN)

- . It like ulnar distribution
- · Arise beneath flexor retinaculum
- Supply all interosseous muscles and lumbrical muscles except first lumbrical







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# Arterial system, venous system and lymphatic drainage of lower

### **Femoral Artery**

- The major artery supplying the lower limb is the femoral artery
- Femoral artery enters the thigh from behind the inguinal ligament as a continuation of extension artery
- · Femoral artery aneurysm present as a pulsatile mass below the inguinal ligament
- \* Branches
  - Superficial circumflex iliac artery
  - Superficial epigastric artery
  - Superficial external pudendal artery
  - Deep external pudendal artery
  - Profunda femoris artery :
    - ✓ Largest branch form lateral side of the femoral artery in the femoral triangle
    - ✓ Branches
      - Medial femoral circumflex artery
      - o Lateral femoral circumflex artery
      - o Four perforating arteries: three of these arise as branches of Profunda femore artery and it end by becoming the 4<sup>th</sup> perforating artery

### Naseem Sherzad High-Yield Points

### Mid-inguinal point

### Mid-point of the inguinal ligament

Mid-inguinal point – halfway between the pubic Symphysis and the anterior superior iliac spine. The femoral pulse can be palpated at this point

Mid-point of the inguinal ligament – halfway between the pubic tubercle and the anterior superior iliac spine (the two attachments of the inguinal ligament). The opening to the inguinal canal is located just above this point

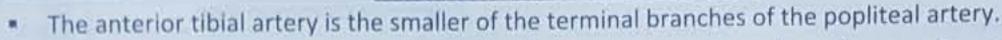
### Inguinal ligament

Attached to the pubic tubercle and anterior superior iliac spine

### **Popliteal Artery**

- Enter the popliteal fossa through opening in adductor magnus as a continuation of femoral artery
- It ends at the level of lower border of the popliteus muscle into anterior and posterior tibial
- Most deeply or most anteriorly placed structure in the popliteal fossa
- Supracondylar fracture of the distal femur can harm popliteal artery
- Pain in calf muscle after walking for 100 yards-----popliteal artery

### **Anterior Tibial Artery**



- It arises at the level of the lower border of the popliteus muscle and passes forward into the anterior compartment of the leg through an opening in the upper part of the interosseous membrane
- It lies superficially in front of lower end of the tibia
- Commonly injured in neck of fibular fracture
- Having passed behind the superior extensor retinaculum, it has the tendon of the extensor hallucis longus on medial side and the tendon of extensor digitorum longus on lateral side. It is here that it pulsation can easily be felt in living human.
- In front of the ankle joint, the artery becomes dorsalis pedis artery

### Dorsalis pedis artery:

- ✓ Terminal branches of anterior tibial artery
- ✓ It passes through 1st and 2<sup>nd</sup> metatarsal space
- ✓ Absent in some children
- ✓ If absent alternate is perforating branches of peroneal artery or accessory peroneal artery
- ✓ Here there is Maximum pulse pressure and maximum amplitude
- ✓ Clinical notes:
  - The pulse of the dorsalis pedis artery on the dorsal surface of the foot can be felt by gently palpating the vessel against the underlying tarsal bones between the tendons of extensor hallucis longus (medially) and the tendon of extensor digitorum longus (laterally) to the second toe.

### **Posterior Tibial Artery**

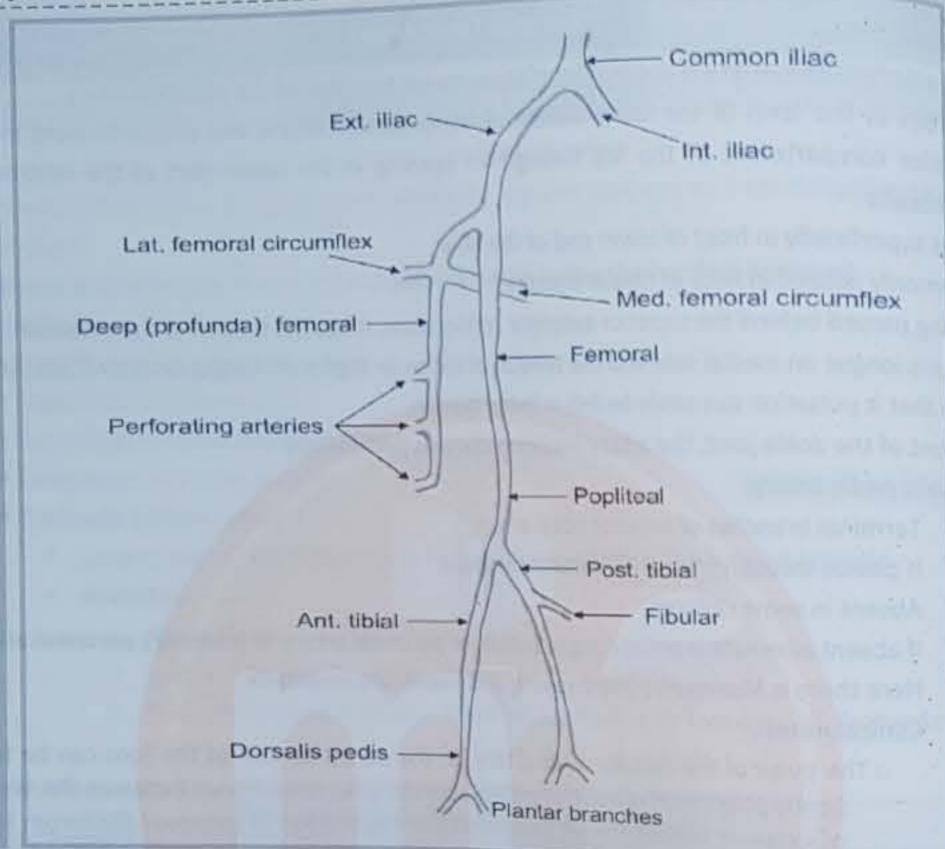
- The posterior tibial artery is one of the terminal branches of the popliteal artery. It begins at the level of the lower border of the popliteus muscle and passes downward deep to the gastrocnemius and soleus and the deep transverse fascia of the leg
- Midway between the medial malleolus and the heel, the pulse of the posterior tibial artery is palpable because here the artery is covered only by a thin layer of the retinaculum, by superficial connective tissue, and by skin
- The artery passes behind the medial malleolus deep to the flexor retinaculum and terminate by dividing into:

### ✓ Medial plantar arteries

- o Smaller terminal branch of the posterior tibial artery
- o It end by supplying the medial side of the big toe

### ✓ Lateral plantar arteries

- Larger terminal branch of the posterior tibial artery
- On reaching the fifth metatarsal bone, the artery curve medially and form the plantar arch and at the first intermetatarsal space joins the dorsalis pedis artery



## Blood Supply of Femur (Head & Neck)

- · Head:
  - Adult: Retinacular artery, a branch of the medial circumflex artery
  - Children: From nutrient artery branch of Obturator artery
- Neck
  - Medial circumflex femoral artery
  - lateral circumflex femoral artery

### **Anastomosis**

- Trochanteric Anastomosis: SLIM
  - Superior Gluteal Artery
  - Lateral femoral circumflex artery
  - Inferior Gluteal Artery
  - Medial femoral circumflex artery
- Cruciate Anastomosis: FILM
  - First perforating artery———a branch of Profunda femoris artery

  - Lateral femoral circumflex artery
  - Medial femoral circumflex artery

Lower Limb

### Venous Drainage

### **Great Saphenous Vein**

- It is the longest vein in the body and has 20 valves
- At the ankle, it is located 2.5cm front/anterior to the medial malleolus
- Ascend with the saphenous nerve in the superficial fascia over the medial side of the leg
- Pass behind the knee and then on the medial side of the thigh
- Enter the saphenous opening

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End: Join the femoral vein about 3.5-4 cm below and lateral to the pubic tubercle

#### Tributaries:

- Medial marginal vein of the big toe
- ✓ The Anterior vein of leg.
- ✓ Superficial Dorsal vein of penis,—deep dorsal vein of penis drain into prostatic venous plexus also known as Santorini's plexus
- ✓ Drain the medial side of the dorsal venous arch of the foot
- ✓ Superficial epigastric vein
- ✓ Superficial circumflex iliac vein
- ✓ The external pudendal veins (deep pudendal & superficial pudendal) are veins of the pelvis, which drain into the great saphenous vein
- ✓ Deep external pudendal vein (last tributary) empties the blood from the anterior part of the perineum.
- ✓ Not receive veins from the deep vein of calf

### Clinical significance:

- ✓ Location in front of medial malleolus should be remembered for emergency blood transfusion and this is also the site for venesection. Notice that, in front of the medial malleolus, the saphenous nerve is located in front of the vein. Thus, during the cut-down process, the saphenous nerve ought to be recognized to avert its injury.
- Great saphenous vein graft: In coronary bypass surgery to ease the ischemia of the heart, a section of the great saphenous vein is removed and utilized for aortocoronary grafting to bypass an arterial obstruction
- Perforator connects the superficial veins with deep veins, which are not present below the inguinal ligament. There are about 5-perforator vein along the great saphenous vein: - 1 in mid-thigh, 2 below the knee, 3, 4, 5 near the lower leg and ankle. The Great saphenous vein itself drain into the femoral vein below the inguinal ligament
- ✓ A saphenous varix is a dilation of the saphenous vein at its junction with the femoral vein in the groin. Soft and compressible and disappear immediately on lying down

### Small Saphenous Vein

- · Arise from the lateral part of the dorsal venous arch
- It ascends behind the lateral malleolus in company with sural nerve
- It runs in the middle of the back of the leg
- The vein pierces the deep fascia and pass between the head of gastrocnemius muscle in the lower part of the popliteal fossa
- End: it ends in the popliteal vein
- Posteromedial femoral vein is sometime called the accessory saphenous vein

# Lymphatic drainage of lower Limb

### 1) Deep inguinal lymph node

Drain Glans of penis and corpora

### 2) Superficial inguinal lymph node

Pass through saphenous opening and drain into deep inguinal lymph node

### Vertical group:

Receive lymph from vessels of lower limb

### Horizontal group:

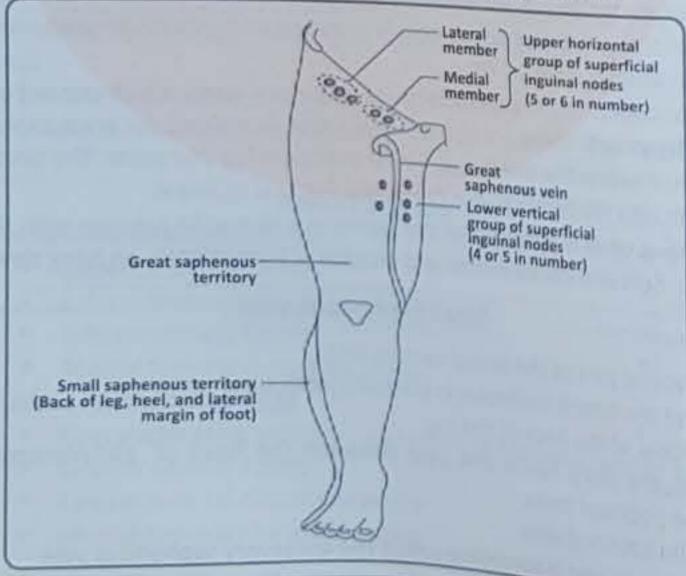
- \* Lateral group:
  - ✓ Receives lymph's from back below iliac crest

### Medial group:

- ✓ Drain from the anterior abdominal wall at the level of the umbilicus and from the perineum
- ✓ From area below the hymen
- ✓ From external genitalia and urethra of both sexes but not from testes.
- ✓ The Lower half of anal canal below the pectinate line
- ✓ Uterus Partially to superficial inguinal lymph node
- ✓ Tunica vaginalis
- ✓ Scrotum

### 3) Popliteal node:

- In addition to the inguinal nodes, there is a small collection of deep nodes posterior to the knee close to the popliteal vessels. These popliteal nodes receive lymph from superficial vessels, which accompany the small saphenous vein, and from deep areas of the leg and foot.
- They ultimately drain into the deep and superficial inguinal nodes.



### Clinical Pearls

### Locking and Unlocking muscle of Knee joint



Lower Limb

### Locking-----

- Locking occurs as a result of medial rotation of femur during the last stage of extension
- Produced by Quadriceps femoris

### Unlocking----

- Unlocking occurs as a result of lateral rotation of femur during the initial stage of flexion
- Produced by Popliteus
- \* When standing, the knee joint is 'locked' into position, thereby reducing the amount of muscle work needed to maintain the standing position

### Common Fractures in lower limb



### The Neck of fibula fracture

- Nerve injure: Common peroneal nerve
- Artery injure: Anterior tibial artery
- Always prefer medial side for bone marrow biopsy in order to save the above structure at the neck of the fibula

#### Femoral Neck Fracture

- Avascular necrosis (AVN) of the Femoral head is a pathological process that results from interruption of blood supply to the bone
- Avascular necrosis (AVN) common in femoral neck fracture and Medial circumflex femoral artery mostly involved
- In the Neck of femur fracture, the affected leg may be shortened and externally or laterally rotated (HIP dislocation: Posterior dislocation Clinical Features: short leg, abducted, internally rotated and slightly flexed leg. Anterior dislocation clinical features: externally rotated, abducted and slightly flexed leg)
- Pain is exacerbated by rotation of the hip



### Direct inguinal hernia:

- The sac of direct inguinal hernia bulge directly anteriorly through the posterior wall of the inguinal canal medial to the inferior epigastric vessels
- Common in old men with weak abdominal muscle
- There is an increased incidence in patient with chronic cough and prostatic obstruction
- The neck of the hernia sac is wide and rarely undergo strangulation

### Indirect inguinal hernia

- The indirect hernia is the most common form of hernia
- It is the remains of process vaginalis and therefore is congenital in origin
- More common on right side
- The hernia sac enters the inguinal canal through deep inguinal ring and lateral to the inferior epigastric vessels.
- The neck of the hernia sac is narrow
- In inguinal hernia repair, the most common structure seen is Pampiniform plexus

### Chapter 8

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Lower Limb

# Direct inguinal Hernia: mnemonics MOAD

- Medial to inferior epigastric artery
- Old age (common in old age)
- Acquired
- Direct inguinal hernia

### Indirect inguinal hernia: mnemonics: LI and CI

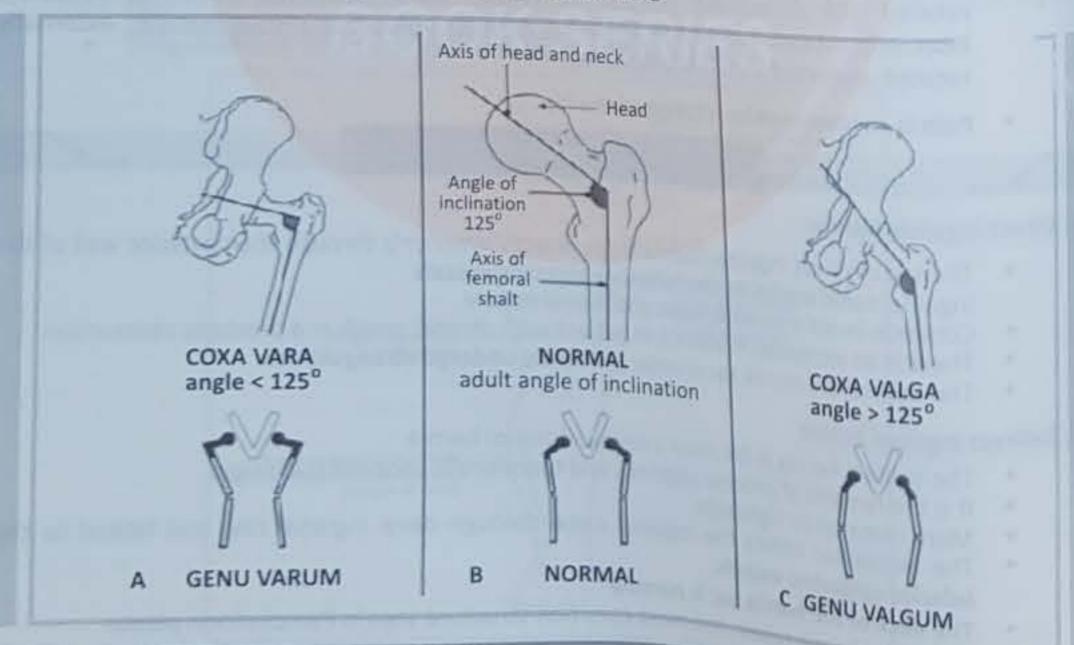
- Lateral to inferior epigastric artery
- Indirect inguinal hernia
- Congenital
- Infancy (common in infant and children)

#### Femoral hernia

- The neck of the sac always lies below and lateral to the pubic tubercle
- The femoral vein lies immediately lateral to the femoral canal. Careful attention to this structure is essential in the repair of femoral hernia
- More common in women than in men
- The incidence of strangulation in femoral hernia is high due to narrow canal. Therefore, all femoral hernias, even asymptomatic ones, should be repaired
- The neck of hernia lies at the femoral ring and at that point related to the boundaries of the femoral ring given above in this chapter.

### Coxa valga and Coxa vara

- The neck of the femur is inclined at an angle with the shaft
- The angle is about 160° in the young child and 125° in the adult
- Coxa valga: A increase in the angle is referred to as Coxa valga
- Coxa vara: A decrease in angle is referred to as Coxa Vara



### Lower Limbs and Genitalia dermatome

The dermatomes of the lower limbs are distributed in spiral arrangements with segments L1-S5. This is because of how the limbs rotate to adopt an erect position during development. Of note, dermatomes S1, S4, and S5 are only on the posterior aspect.

- L1 posteriorly includes the skin lateral to the L1 vertebra and wraps anteriorly to the groin and pelvic girdle area superior to the inguinal canal
- . L2 anteriorly covers the thigh inferior to the inguinal canal
- ❖ L3 evenly spaced between L2 and L4, extending down the medial aspect of the thigh and leg
- L4 anteriorly curves from the lateral aspect of the thigh to the medial aspect of the leg and foot. Includes the knee (skin over the knee), medial surface of the big toe, and medial malleolus
- . L5 Posterolateral aspect of the thigh wrapping anteriorly at the level of the knee to cover the anterolateral aspect of the leg. Includes the dorsal and plantar aspects of the foot, lateral surface of the big toe, and toes, 2, 3, and 4: in easy words L5 for the big toe and S1 for small toe
- \* S1 extends to the posterolateral aspect of the thigh, popliteal region, and leg to the lateral malleolus, lateral margin of foot, heel, and the little toe
- \* 52 extends from the buttocks to the posteromedial aspect of the thigh, popliteal region and leg. Anteriorly includes the penis and scrotum
- \* S3 posteriorly includes the medial aspect of buttocks, perineal area; anteriorly includes the penis and scrotum
- \$4 perineal area, and genitals
- S5 perineal area, and skin of and adjacent to the anus
- ❖ knee jerk------L3-L4

- . The weakness of plantar flexion, difficulty in toe walking, Achilles reflex----L5-S1

# Interesting Facts

- Funny Bone-
- Musician nerve------Ulnar nerve @ Widow artery------Proximal LAD
- Tailors muscle (longest muscle) ------Sartorius
- Smallest muscle-----Stapedius
- Strongest muscle-----Tongue
- Largest vein-----IVC
- Largest artery------Aorta
- Longest bone-----Femur
- Smallest bone-----Stapes
- Largest organ-----Skin
- Peripheral heart of human body------Soleus muscle of leg (skeletal muscles pump)
- Obturator externus-----run inferiorly to hip joint

### **Lumbar Plexus**

- The lumbar plexus is a network of nerve fibers that supplies the skin and musculature of the low limb. It is located in the lumbar region, within the substance of the psoas major muscle an anterior to the transverse processes of the lumbar vertebrae.
- The plexus is formed by the anterior rami (divisions) of the lumbar spinal nerves L1, L2, L3 and It also receives contributions from thoracic spinal nerve 12.

#### Branches

### 1) Iliohypogastric Nerve

THE RESERVE THE PERSON NAMED IN COLUMN 1 I

- The Iliohypogastric nerve is the first major branch of the lumbar plexus. It runs to the liquid crest, across the quadratus lumborum muscle of the posterior abdominal wall. It the perforates the transversus abdominis, and divides into its terminal branches.
- Roots: L1 (with contributions from T12)
- Motor Functions: Innervates the internal oblique and transversus abdominis.
- Sensory Functions: Innervates the posterolateral gluteal skin in the public region. (Tip: an ease way to remember that the IlioHypogastric comes before the IlioInguinal is that H come before I in the alphabet!)

### 2) Ilioinguinal Nerve

- The ilioinguinal nerve follows the same anatomical course as the larger iliohypogastric new After innervating the muscles of the anterior abdominal wall, it passes through the superficitinguinal ring to innervate the skin of the genitalia and middle thigh.
- Roots: L1.
- Motor Functions: Innervates the internal oblique and transversus abdominis.
- Sensory Functions: Innervates the skin on the upper middle thigh. In males, it also supplies the skin over the root of the penis and anterior scrotum. In females, it supplies the skin over the sk

### 3) Genitofemoral Nerve

- After leaving the psoas major muscle, the genitofemoral nerve quickly divides into a genital branch, and a femoral branch.
- Roots: L1, L2.
- Motor Functions: The genital branch innervates the cremasteric muscle.
- Sensory Functions: The genital branch innervates the skin of the anterior scrotum (in males) or the skin over mons pubis and labia majora (in females). The femoral branch innervates the skin on the upper anterior thigh.

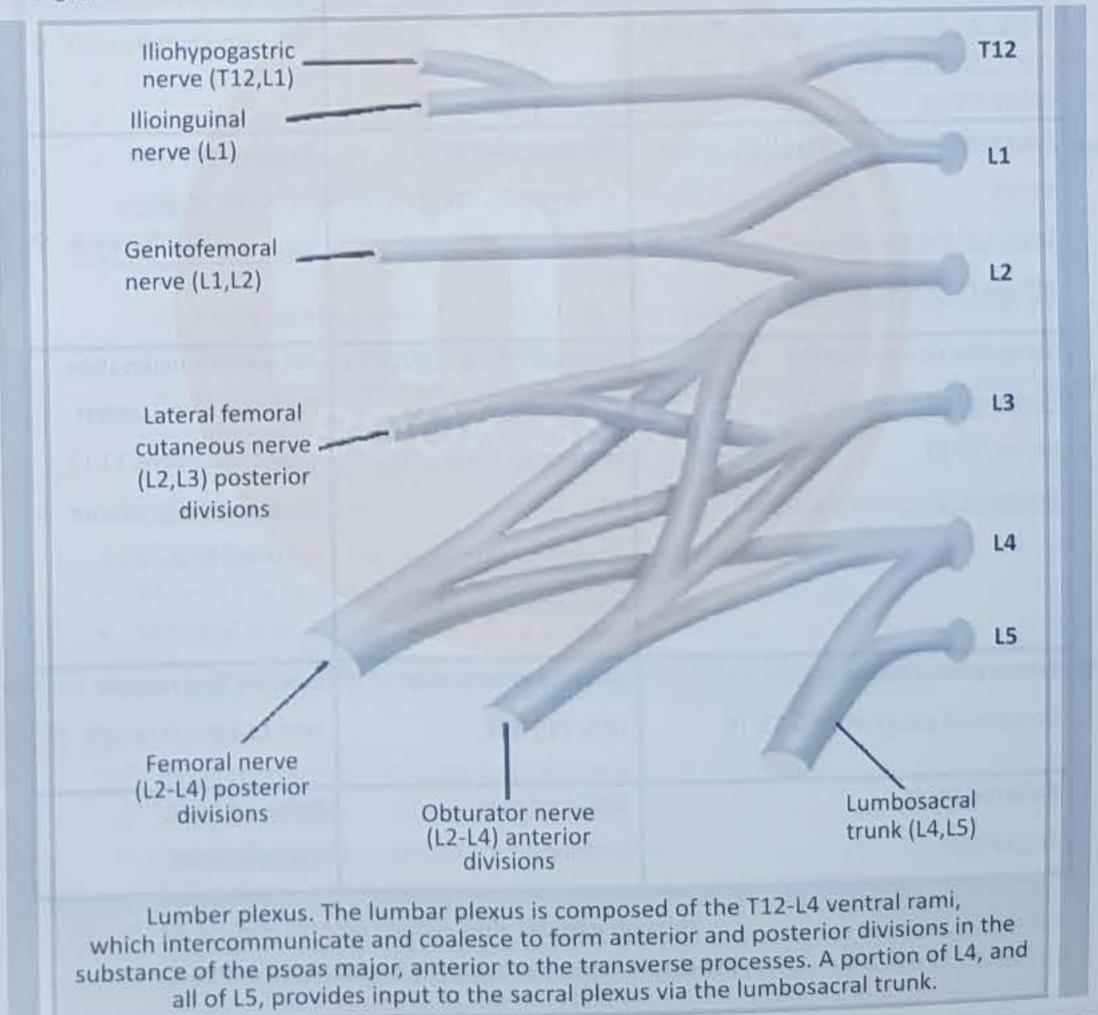
### 4) Lateral Cutaneous Nerve of the Thigh (also called the lateral femoral cutaneous nerve)

- This nerve has a purely sensory function. It enters the thigh at the lateral aspect of the inguinal ligament, where it provides cutaneous innervation to the skin there.
- Roots: L2, L3

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- Motor Functions: None.
- Sensory Functions: Innervates the anterior and lateral thigh down to the level of the knee.
- Meralgia paresthetica is caused by the compression of the lateral cutaneous nerve of thigh.
- The lateral femoral cutaneous nerve is visible in the laparoscopic approach to the hernia repair. This nerve can be injured in placement of the mesh used for repair, especially if staples are used
- 5) Note: A useful memory aid for the branches of the lumbar plexus is: I, I Get Leftovers On Fridays.

  This stands for the Iliohypogastric, Ilioinguinal, Genitofemoral, Lateral cutaneous nerve of the thigh, Obturator and Femoral.



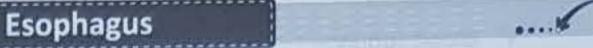
**GIT Anatomy** 

### CHAPTER

# GIT ANATOMY

FOREGUT	MIDGUT	HINDGUT
Artery: Celiac Artery  Body of the spleen is not derived from foregut but supplied by the celiac artery	Artery: 5MA	Artery: IMA
Parasympathetic innervation, vagus nerve Lesion of the parasympathetic system affects mostly GI muscles	Parasympathetic innervation, vagus nerve	Parasympathetic innervation, pelvic splanchnic nerve, S2-4
Preganglionic: Greater splanchnic nerve, T5-T9 Postganglionic: celiac ganglion	Sympathetic innervation Preganglionic: Lesser splanchnic nerve, T10- T11 Postganglionic: superior mesenteric ganglion	Preganglionic: Lumbar splanchnic nerve, L1-L2 Postganglionic: inferior mesenteric ganglion
Sensory innervation  Dorsal root ganglion DRG T5-T9  Referred pain:	Sensory innervation  DRG T10-T11  Referred pain:	Sensory innervation  DRG L1-L2  Referred pain:

### Fsonbagu



Muscular tube about 10 inches (25 cm) extending from pharynx to stomach

 Begin at the lower border of cricoid cartilage (C6), pass through the diaphragm at T10 level to enter the stomach

It is collapsed at rest

Chapter 9

- Dilation or enlargement of left atrium cause esophageal obstruction or dysphagia
- · Esophagus pass through left Crus of the diaphragm with the sling of fibers from right crus

### **Esophageal Constriction**

Normally, there are 4 sites of anatomical constriction/narrow parts in the esophagus. The distance of each constriction is measured from upper incisor teeth. The constrictions are as follows

### Cricopharyngeus:

- ✓ First constriction
- √ 15 cm (6 inches) from the upper incisor teeth
- ✓ This is the narrowest portion of the esophagus and approximately corresponds to the sixth cervical vertebra

### Aorticobronchus

- ✓ Divide into
  - Aortic constriction----2<sup>nd</sup> constriction, at crossing of arch of aorta, vertebral level---- T4----22 cm from the upper incisor teeth
  - o Bronchial constriction----middle one------3<sup>rd</sup> constriction, at crossing of left principal bronchus, vertebral level----T6-----
  - o 27 cm from the upper incisor teeth

### Diaphragmatic constriction

- √ 4<sup>th</sup> constriction
- √ 40 cm (15 inches) from the upper incisor teeth
- ✓ Vertebral level-----T10

### Blood supply, Venous drainage, Lymph drainage and Histology

### 1) Upper third:

- ✓ Blood supply:-----Inferior thyroid artery
- ✓ Venous drainage:----Inferior thyroid vein
- ✓ Lymph drainage:-----Deep cervical lymph node
- ✓ Epithelium: -----Stratified squamous non keratinized epithelium
- ✓ Muscularis externa contain only skeletal muscles
- ✓ Common carcinoma: Squamous cell carcinoma (15%)

**GIT Anatomy** 

### 2) Middle third

- ✓ Blood supply:———Descending thoracic aorta
- ✓ Venous drainage:——Azygos vein
- ✓ Lymph drainage: -----Superior and posterior Mediastinal lymph node
- ✓ Epithelium: -----Stratified squamous non keratinized epithelium.
- ✓ Muscularis externa contains combination of skeletal muscles and smooth muscles
- ✓ Common carcinoma: Squamous cell carcinoma (50%)

### 3) Lower third

- ✓ Blood supply——Left gastric artery
- ✓ Venous drainage-----Left gastric vein
- ✓ Lymph drainage——Node along left gastric vessels and celiac vessels
- ✓ Epithelium: ----- Stratified squamous non keratinized epithelium.
- Muscularis externa contain only smooth muscles
- ✓ Common carcinoma: Adenocarcinoma

### Histology

- . The wall of the esophagus consists of four layers: Mucosa, Submucosa, Muscularis propria, am Adventitia. Unlike other areas of the Gl tract, the esophagus does not have a distinct serosa covering
- . The average life of gastrointestinal epithelium is 2-7 days

### Gastroesophageal Sphincter

- \* No anatomic sphincter exists at the lower end of the esophagus. However, the circ smooth muscle in this region serves as a physiologic sphincter.
- . Metachlorpromide maintain the competence of gastroesophageal junction
- It relaxes during swallowing

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- . At rest, the esophagus is closed at both ends by the upper esophageal sphincter at the top and the lower esophageal sphincter at the bottom.
- . Lower Esophageal Pressure (LEP):
  - ✓ Increased by: Gastrin, Motilin, substance-P, vasopressin, glucagon
  - ✓ Decreased by: secretin, G.I.P, V.I.P, CCK, progesterone

### Deglutition (Swallowing)

Deglutition: Deglutition is the process by which food is passed from mouth through the pharynx and esophagus into the stomach as a result of reflex phenomena. Deglutition can be divided into three parts:

### 1) Voluntary stage:

Bolus ready for swallowing → Pressure of the tongue upward and backward against the palate →

Bolus forced by the tongue into the pharynx

### 2) Pharyngeal stage (involuntary):

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Bolus in the posterior mouth stimulates swallowing receptor area around the opening of pharynx → Afferent impulses are transmitted through 9th (Glossopharyngeal) and 10th (vagus) cranial nerves to swallowing center in medulla and lower pons → Efferent impulses pass to the pharynx and upper esophagus to cause the following effects:

- The Soft palate is pulled upward to close the posterior nares.
- Palatopharyngeal folds are pulled medially to form a sagittal slit which allows properly masticated food to pass and prevents large particles to pass through it.
- Vocal cords are approximate(adduct) and larynx is pulled upward and anteriorly by neck muscle
- ✓ Since the true vocal folds adduct during the swallow, a finite period of apnea (swallowing) apnea) must necessarily take place with each swallow
- ✓ Peristalsis begins in the pharynx, which propels the food from pharynx into the esophagus.

### 3) Esophageal stage or third part of deglutition (involuntary):

During this stage, food moves through esophagus into the stomach. Three factors participate in it:

- Primary Peristalsis: It is a continuation of the peristaltic waves that begin in the pharynx. It propels most of the bolus into the stomach.
- ✓ Secondary Peristalsis: The remaining bolus in the esophagus causes distension of the esophagus -> Vagal reflex occurs which initiates secondary peristalsis in esophagus, and causes receptive relaxation of LES -> The remaining bolus is passed into the stomach.
- Gravity (in standing position): Gravity increases the rate of passage of food through the esophagus but the movement of food in esophagus does not depend upon gravity; food will still reach the stomach even if the person is upside down.

### **Naseem Sherzad High-Yield Points**

- \* The swallowing reflex is coordinated in the medulla. Fibers in vagus and Glossopharyngeal nerves carry information between the GIT and the medulla.
- The soft palate moves upward to close the posterior nares.
- The secondary peristaltic wave clears the esophagus of any remaining food.
- . Gravity accelerates the rate of passage of food through the esophagus but the passage of food through the esophagus is not dependent on gravity.
- The gastroesophageal sphincter relaxes during swallowing.
- During swallowing, the Palatopharyngeal folds move medially
- . The Mixing wave of stomach originate in the body of the stomach
- \* Esophageal stage of swallowing is affected by Scleroderma

### Stomach

The stomach is relatively fixed at both ends but is very mobile in between.

### Histology:

- Epithelium----Simple columnar epithelium
- No goblet cell

### Parts:

- Fundus: This is dome-shaped and projects upward and to the left of the cardiac orifice. Its usually full of gas.
- . Body: This extends from the level of the cardiac orifice to the level of the incisus angularis, a constant notch in the lower part of the lesser curvature
- Pyloric antrum: This extends from the incisura angularis to the pylorus
- Pylorus: This is the most tubular part of the stomach. The thick muscular wall is called the pyloric sphincter, and the cavity of the pylorus is the pyloric canal. The Circular muscle becomes thickened at the level of pylorus and forms sphincter

### Gastric gland:

### Parietal cell (Oxyntic cell):

- These cells are located in the gastric glands found in the lining of the fundus and in the cardia of the stomach.
- Secrete HCL and intrinsic factor of castle (glycoprotein)
- Contain copious Eosinophilic cytoplasm and central nucleus
- ✓ Parietal cells contain receptor for: Gastrin, Histamine (H2) and acetylcholine(M3)
- ✓ Somatostatin is the major paracrine hormone that inhibits gastric HCL secretion
- ✓ PPI: Irreversible bind to H<sup>+</sup>/K<sup>+</sup> ATPase enzyme, cause blocking of all gastric acid secretion
- Antihistamine: Block histamine receptors in Parietal cell, resulting in decreased acid production.
- ✓ Gastric acid production inhibitors: Low Ph <3, Prostaglandin and Somatostalin
- ✓ Most of the drugs are advised to be taken after meals to reduce gastni irritation/upset
- ✓ Daily secretion and Ph of gastric juice: daily secretion: 1200 to 1500ml and Ph: 0.5 to 1.5
- ✓ The carbon-labeled urea breath test is the non-invasive method of choice to document eradication of a H pylori infection

### · Chief (peptic) cell

- √ Secret Pepsinogen
- ✓ Pepsinogen is converted into pepsin by HCL, which causes digestion of protein.
- Pepsin has a very acidic Isoelectric point and is stable in acidic solution below ph 6, but it is irreversibly denatured at pH 7 or above. In contrast, Pepsinogen is stable in neutral or slightly alkaline solution.
- ✓ Abundant in fundus of stomach

### · Mucoid cell:

- ✓ Provide protective mucous coat
- ✓ Protect against self-digestion by HCL

### Wenous drainage:

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- The veins drain into the portal circulation.
- The left and right gastric veins drain directly into the portal vein.
- The short gastric veins and the left gastroepiploic veins join the splenic vein.
- The right gastroepiploic vein joins the superior mesenteric vein.

### Lymph drainage:

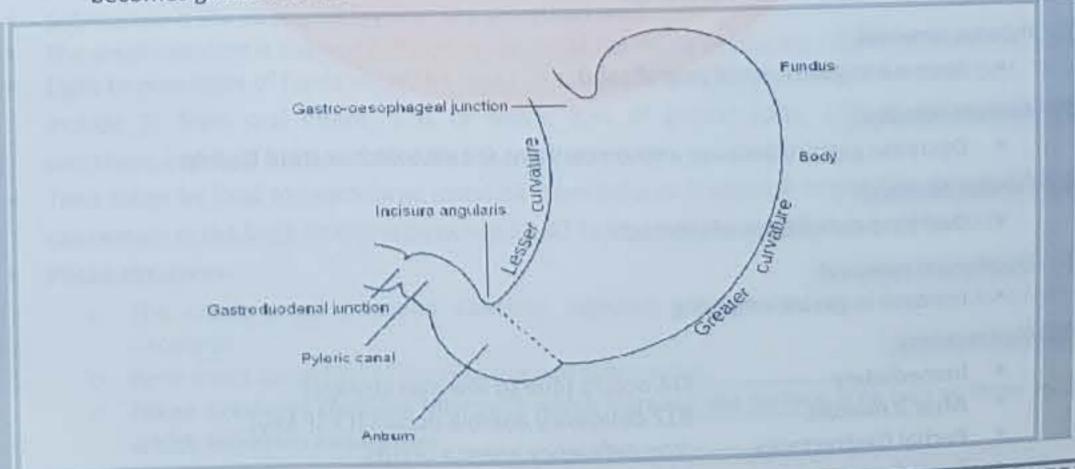
- The lymph vessels follow the arteries into the left and right gastric nodes, the left and right gastroepiploic nodes, and the short gastric nodes.
- All lymph from the stomach eventually passes to the celiac nodes located around the root of the celiac artery on the posterior abdominal wall.
- Blood supply of stomach is given under the topic of "Celiac Trunk" with a diagram at the end of this chapter

### Celiac plexus:----Solar plexus

- ♦ The Celiac plexus is the largest of the autonomic plexuses and is located on the anterior side of the aorta around the beginning of the celiac trunk and superior mesenteric artery
- ♦ The celiac plexus contains the visceral afferent and efferent fibers from T5 to T12 by means of the greater splanchnic nerves (T5/T6 to T9/T10), lesser splanchnic nerves (T10/T11) and least (T11/T12) splanchnic nerves
- It lies over the anterio-lateral surface of aorta at the T12/L1 vertebral level

### Embryology:

- Develop as a fusiform dilatation of the caudal part of the foregut in the middle of 4th week
- Initially oriented in the midline
- During the next 2 weeks, the right wall of the swelling grows more rapidly than the left wall
- The Stomach rotates at the start of 5th week.
- This leads to the formation of the future greater omentum and lesser curvature of the adult stomach
- The anterior/ventral border become lesser curvature and the posterior/dorsal border becomes greater curvature



# **Surgeries and Outcome**

### 1) Esophagectomy:

- Mobilization of the stomach must be done with care as it is essential to have a tension free well-vascularized stomach for transposition
- The left gastric, short gastric and left gastroepiploic arteries all are divided
- The viability of the transposed stomach mainly depends on the right gastroepiploic arten and, to lesser extent on, the right gastric vessels
- It should be noted that venous drainage is as important as arterial supply to perform a accurate anatomical dissection that preserves the right gastroepiploic vein as well as the artery

### 2) Truncal Vagotomy:

- . The principle of the Truncal Vagotomy is that section of the vagus nerve, which is critically involved in the secretion of gastric acid, reduce the maximal acid output by 50%.
- Following Truncal vagatomy and selective gastric motility and gastric emptying decrease
- Fulminant diarrhea may be a problem after vagatomy (it is one of the many complications collectively known to as post-vagatomy syndromes). It occurs in 1-2% of patients following Truncal vagatomy and is less likely to be found after selective or highly secretive vagatomy

### 3) Selective vagatomy:

- Vagatomy with sparing the hepatic branch of the anterior vagus and celiac branch of the posterior vagus
- Complication: delay gastric emptying

### 4) Highly selective Vagotomy:

- The unpleasant effect of surgery were largely avoided, although loss of receptive relaxation of the stomach did occur, leading to epigastric fullness and sometimes mild dumping
- The nerves supply to the pylorus is left intact and therefore no drainage procedure is required (no problem of gastric emptying). The complication rate is lower

### 5) Thoracic Vagotomy:

- Decrease gastric acid secretion
- 6) Pylorus removal:
  - Increase in gastric emptying of solid
- 7) Antrum removal:
  - Decrease gastrin, because antrum contains G-cells which secrete Gastrin
- 8) Fundus removal:
  - Decrease compliance of stomach
- 9) Duodenum removal:
  - Increase in gastric emptying
- 10) Gastrectomy:
  - -IDA occurs (due to low iron storage) Immediately-
  - -B12 deficiency anemia occurs (CPSP key). After 3 months-
  - -Iron deficiency anemia occurs Partial Gastrectomy-
  - -B12 deficiency anemia occurs (treatment is I/V Vit-B12) Total Gastrectomy-

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**GIT Anatomy** 

### 11) Subtotal Gastrectomy:

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- About 80% of the distal stomach is removed
- 12) Complete removal of the colon:
  - Cause electrolyte imbalance
- 13) Complete Denervation of small intestine results in:
  - Paralytic ileus
- 14) Ileostomy, colostomy, jejunostomy
  - Jejunostomy:
    - ✓ Cause osmotic diarrhea
  - Ileostomy:
    - ✓ An ileostomy is spouted, a colostomy is flush
    - lleostomy effluent is usually liquid, whereas colostomy effluent is usually solid
    - ✓ Ileostomy is usually sited in the right iliac fossa, end colostomy is sited in the left iliac fossa
    - ✓ Commonest and early complication is fluid and electrolyte loss, cause osmotic diarrhea
  - Colostomy:
    - ✓ Cause secretory diarrhea
    - Most common serious complication of end colostomy is skin breakdown
    - ✓ Causes hypokalemia
  - Up to 50% of the small intestine can be surgically removed or bypassed without permanent deleterious effects.
  - · Short bowel syndrome is often defined as that symptoms complex occurs in adult who have less than 200cm of combined jejunum-ileum following small bowel resection

### Small Intestine and Large Intestine differences

### 1) Small Intestine

- Drain into celiac and superior mesenteric lymph node
- Blood supply: Superior mesenteric artery (SMA)
- 6m long or 20 feet----Epididymis is also of the same length
- Brunner's gland: Present only in the duodenum
- Submucosa is the strongest layer of the intestinal wall
- The small intestine is the body largest reservoir of hormone producing cells
- Eight to nine liters of fluids enter the small intestine daily of which over 80% is absorbed. This include 2L from oral intake, 1.5L of saliva, 2.5L of gastric juice, 1.5L of biliopancreatic secretions and IL of fluids secreted by the small intestine
- Time taken by food to reach large intestine from pylorus is about 8 hours. The digested food can remain in the large intestine between 12-47 hours until it is expelled out of the body
- Plicae circulares:

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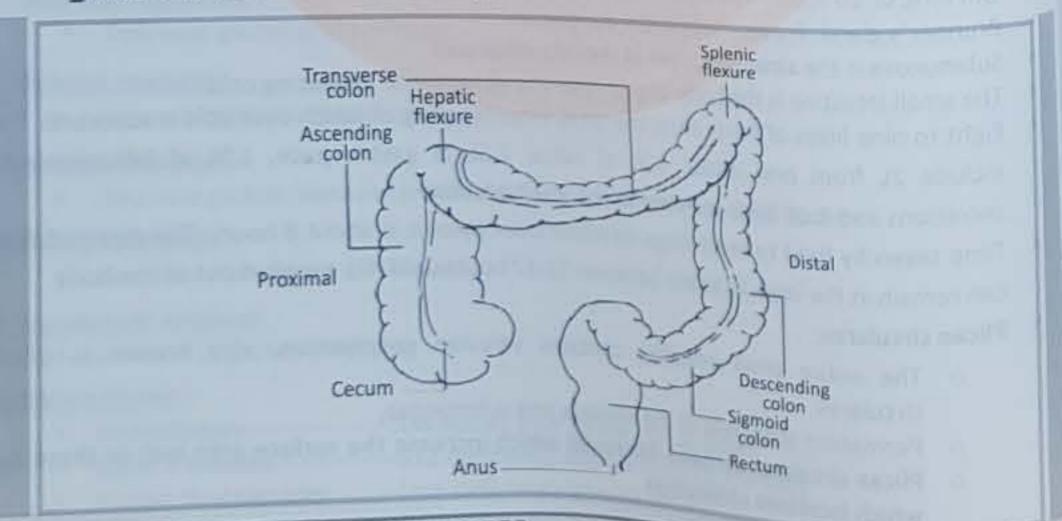
- o The entire small intestine contains valvulae conniventes, also known as plicae circulares
- o Permanent spiral fold of the mucosa and submucosa,
- Plicae circulares contains Microvilli which increase the surface area two or three fold, which increases absorption

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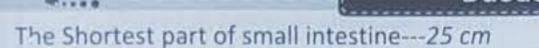
- Crypts of Lieberkühn: contain two types of cell Paneth cell: Secrete anti-microbial peptide and protein, rich in RER, rich in Zinc and
  - contain lysosome
  - o Goblet cell
- Peyer's patches
  - o located in ileum
  - Early infection of typhoid involves payer's patches. Over the course of the first week illness, the notorious gastrointestinal manifestations of the disease develop. Monocolo infiltration inflames Peyer patches and narrows the bowel lumen, causing constipation
  - The gallbladder is the main reservoir during a chronic infection with S. Typhi
- Microfold cell—M-cell—Present in payer patches and sample antigen as well as bacteria-Antigen presenting cell -----
  - ✓ Ileum contains M cells on payer patches, That endocytoses antigens and present then to nearby lymphocytes
  - ✓ ABO Blood grouping is due to the process of these cells.
- Three main differences:
  - ✓ M-cell----antigen presenting cell in payer patches
  - ✓ M-band—formed by plasma cell
  - M-protein: M protein is an important virulence factor expressed on the surface of S. pyogenes

### 2) Large intestine: Mnemonic AST

- . Appendices epiploicae: These are the pouches of peritoneum containing fat, hanging from the colon. Appendices epiploicae are absent from beginning (Caecum and Appendix) and ending (Rectum) of the colon-----CAR
- Sacculation, also called haustration
- Teniae coli—Absent in rectum and appendix



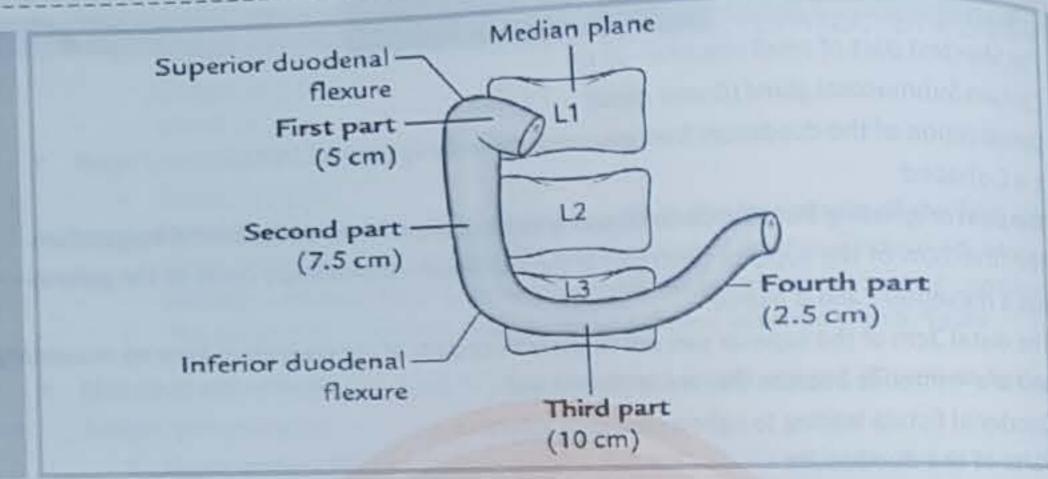
#### Duodenum



- Contain Submucosal gland (Bruner gland)
- Demarcation of the duodenum from jejunum is shown by ligament of treitz
- It is C-shaped
- The pain originating from duodenum is poorly localized and referred to the central epigastrium.
- The first 2cm of the superior (first) part of the duodenum-immediately distal to the pylorus---has a mesentery and is mobile
- The distal 3cm of the superior part and the other three parts of the duodenum have no mesentery and are immobile because they are retroperitoneal
- Duodenal fistula leading to highest electrolyte imbalance
- Parts of the duodenum:
  - ✓ Superior part (Ist part)
    - o The Commonest site for peptic ulcer
    - An ulcer of the posterior wall of the first part of the duodenum may penetrate the wall and erode the relatively large gastroduodenal artery, causing a severe hemorrhage.
    - o It is Surrounded by hepatoduodenal ligament
  - √ Descending (2<sup>nd</sup> part)
    - Duodenum is the second most common site for diverticula in the alimentary tract being the second portion the most frequent location.
    - The second part of the duodenum runs vertically downward in front of the hilum of the right kidney on the right side of the second and third lumbar vertebrae
    - Operations on the colon and right kidney have resulted in damage to the duodenum.
    - O Anterior relations: Transverse colon, the right lob of liver, fundus of gallbladder and coil of the small intestine
    - o Posterior relations: Hilum of the right kidney and right ureter
  - ✓ Horizontal (3<sup>rd</sup> part)-----Longest
    - O Vulnerable to injury as it lies anterior to the vertebral column
    - o The third part of the duodenum may be severely crushed or torn against the third lumbar vertebra
    - Anterior relations: Superior mesenteric vessels, root of mesentery of small intestine, coils of the jejunum
    - Posterior relations: Right ureter and right psoas muscle, IVC and aorta
  - √ Ascending (4<sup>th</sup>part):
    - Paraduodenal recess (fossa): It's the lowest when present. It is located to the left of the fourth part of the duodenum behind the paraduodenal fold of the peritoneum with its orifice facing medially. The paraduodenal fold includes inferior mesenteric vein in its free border edge.

GIT Anatomy

**GIT Anatomy** 



- The jejunum is wider bored, thicker walled, and redder than the ileum
- Drain into the superior mesenteric lymph node
- Supplied by greater and lesser splanchnic nerve
- Feather appearance on barium
- Recognized by single or double arcade arteries

### **Naseem Sherzad High-Yield Points**

Jejunum

- The Maximum absorption of water occurs in jejunum.
- The efficiency of water and salt absorption in the colon exceed 90%.
- Ileum Is critical in the conservation of fluid and electrolyte
- Absorption of folate occurs in the jejunum
- Bile and the fluids found in the duodenum, jejunum and ileum all have an elections content similar to that of ringer lactate
- Saliva, gastric juice and right colon fluids have high K<sup>+</sup> and low Na<sup>+</sup> content
- Pancreatic secretion are high in bicarbonate
- Absorption of long-chain fatty acid occurs in the duodenum and jejunum
- Absorption of short-chain fatty acid occurs in the colon
- Oxidation of both long and short-chain fatty acid occur in peroxisomes

### Terminal ileum

- Aggregations of lymphoid tissue (Peyer's patches) are present in the mucous membrane of the lower ileum along the antimesenteric border. In the living, these may be visible through the wall of the ileum from the outside.
- Bile salts are absorbed through Na-bile acid Co-transport
- Bile salts are absorbed and all and a salts are absorbed and a salts are a salts are absorbed and a salts are a salts a lower quadrant
- Terminal ileal resection sequelae:
  - ✓ The Increase water content of stool—should be on top.
  - ✓ Decrease Bile salt absorption...next

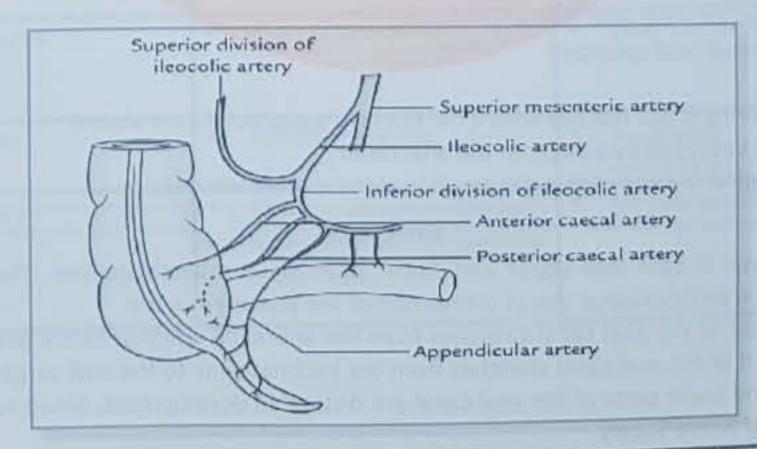
- ✓ Decrease Vit-B12 absorption
- Decrease turnover chenodeoxycholic acid
- Because of interruption of the Enterohepatic cycle of bile salt and hyperoxaluria as a result of the increased absorption of oxalate in the colon predisposing to renal stone

#### \* Ileocecal valve:

- ✓ A rudimentary structure, the ileocecal valve consists of two horizontal folds of mucous. membrane that project around the orifice of the ileum.
- ✓ The valve plays little or no part in the prevention of reflux of cecal contents into the ileum.
- ✓ The circular muscle of the lower end of the ileum (called the ileocecal sphincter by physiologists) serves as a sphincter and controls the flow of contents from the ileum into the colon.
- The smooth muscle tone is reflexly increased when the cecum is distended; the hormone gastrin, which is produced by the stomach, causes relaxation of the muscle tone

### **Appendix**

- The appendix lies in the right iliac fossa, and in relation to the anterior abdominal wall, its base is situated one-third of the way up the line joining the right anterior superior iliac spine to the umbilicus (McBurney's point)
- Blood supply—Appendicular artery is normally branch of the inferior division of ileocolic artery: References: RJ Last, BRS Anatomy, Bailey and Love short Anatomy
- The appendicular branch enters the free margin of the mesoappendix and supply the appendix
- Lymph drainage----Superior Mesenteric lymph nodes
- Acute appendicitis major lab finding...raised TLC and associated with Neutrophilic Leukocytosis
- The Most common position of appendix is Retrocecal and the most common type of intussusceptions is ileocolic
- The Pain of pelvic appendix increase on flexing the thigh
- Appendicitis pain radiate to umbilicus through T-10
- Lamina propria contain large lymphatic nodules that extends into sub-mucosa that's why muscularis mucosa is an incomplete layer
- Embryology: Appendix is derived from the midgut



**GIT Anatomy** 

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- The rectum is about 5 in. (13 cm) long and begins in front of the third sacral vertebra at a continuation of the sigmoid colon
- The puborectalis portion of the <u>levator ani muscles forms a sling at the junction of the rectuments</u> with the anal canal and pulls this part of the bowel forward, producing the anorectal angle,
- The peritoneum covers the anterior and lateral surfaces of the first third of the rectum and only the anterior surface of the middle third, leaving the lower third devoid of peritoneum
- The superior, middle, and inferior rectal arteries supply the rectum.
- The lymph vessels of the rectum drain first into the pararectal nodes and then into inferior mesenteric nodes. Lymph vessels from the lower part of the rectum follow the middle rects artery to the internal iliac nodes.
- . The nerve supply is from the sympathetic and parasympathetic nerves from the inferior hypogastric plexuses. The rectum is sensitive only to stretch.



# Anal Sphincter, Anorectal ring and Anal canal

The internal sphincter is formed from a thickening of the smooth muscle of the circular coat a the upper end of the anal canal. The internal sphincter is enclosed by a sheath of striped muscle that forms the voluntary external sphincter

**Anal Sphincters** 

- The external sphincter can be divided into three parts:
  - ✓ A subcutaneous part, which encircles the lower end of the anal canal and has no bon attachments
  - ✓ A superficial part, which is attached to the coccyx behind and the perineal body in the front
  - ✓ A deep part, which encircles the upper end of the anal canal and has attachments

### Anorectal Ring

- It is formed by the fusion of:
  - ✓ Puborectalis
  - ✓ Deep external anal sphincter
  - √ Internal anal sphincter
- Importance:

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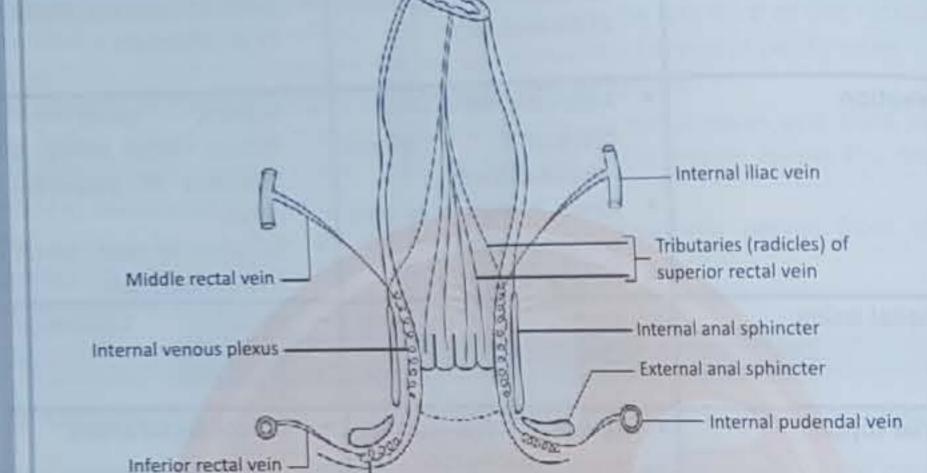
- ✓ The ring is less marked where the fibers of puborectalis are absent
- ✓ It is easily felt by a finger in the anal canal
- ✓ Surgical division of this ring result in rectal incontinence.

### Anal canal

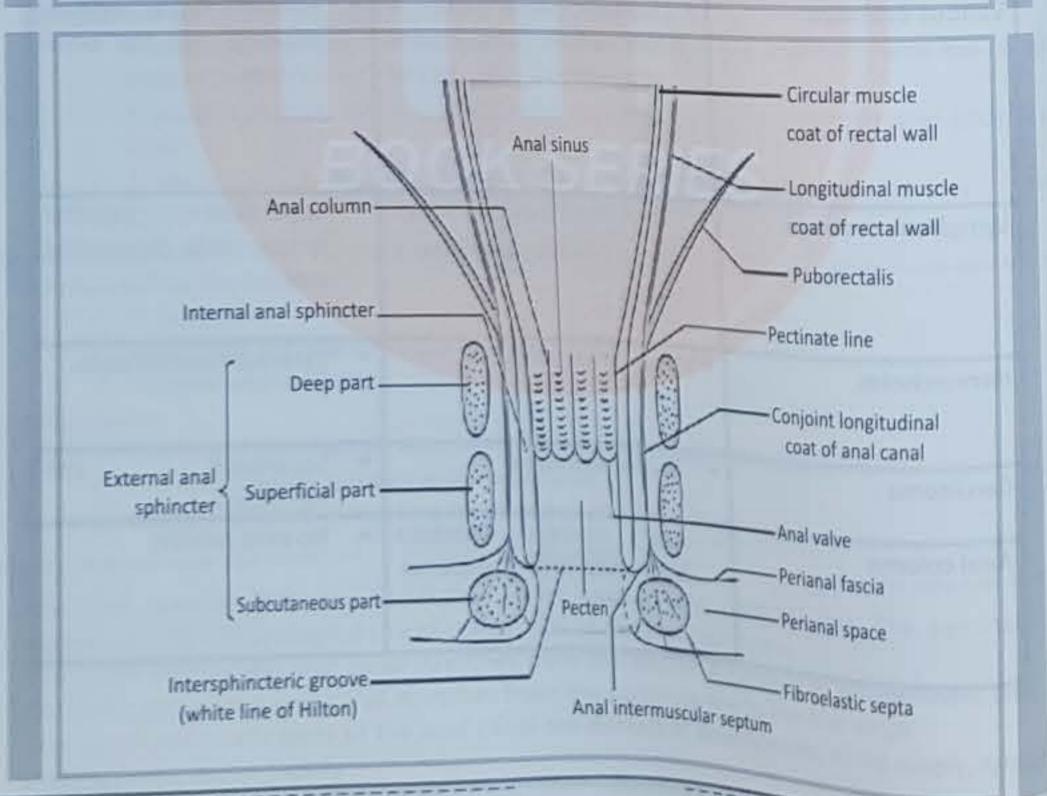
- The anal canal is split into upper and lower parts by the pectinate line. The pectinate line represents the embryological site of connection of the anal membrane.
- represents the embryological represents the embryological canal stretches from the anorectal junction to the pectinate line; and The upper part of the anal canal stretches from the pectinate line to the anal verge.
- the lower part of the anal canal are distinct in development, blood supply, lymphatic drainage, and Nerve Supply

### Difference between the upper and lower anal canal

Features	Upper Anal Canal	Lower Anal Canal
Development	<ul> <li>Develop From endoderm of the hind gut</li> </ul>	Develop From ectoderm     of proctodeum
Innervation	<ul> <li>Autonomic nerve———————————————————————————————————</li></ul>	<ul> <li>Somatic nerve———         Inferior rectal nerve, a         branches of pudendal         nerve</li> <li>Sensitive to pain, touch         and temperature</li> </ul>
Epithelial lining	<ul> <li>Simple columnar epithelium</li> </ul>	Stratified squamous epithelium
Arterial supply	<ul> <li>Superior rectal artery (direct continuation of IMA)</li> </ul>	Inferior rectal artery
Venous drainage	<ul> <li>Superior rectal vein         IMV—which joins splenic         veinenters the portal         vein</li> </ul>	<ul> <li>Inferior rectal vein draining into the caval system</li> </ul>
Lymphatic drainage	<ul> <li>Drain into Pararectal nodes then inferior mesenteric nodes</li> </ul>	<ul> <li>Superficial inguinal lymph node (horizontal set)</li> </ul>
Hemorrhoids	Internal hemorrhoid	External hemorrhoids
Carcinoma	Adenocarcinoma	Squamous cell     carcinoma
Anal column	<ul> <li>Anal column (contain tributaries of the superior rectal vein)</li> </ul>	



External venous plexus



### Liver

#### Introduction

- Liver is the largest gland of the body
- Liver weight 1.5kg----1500 gm

- The Capsule of the liver is called the Glisson capsule which is a peritoneal membrane
- Embryology: Liver develop from the ventral mesentery of distal foregut
- Liver is 4% in the fetus and 5% in the newborn, of the total body weight and occupies more space in the abdominal cavity.
- The liver is relatively much larger in the child than in the adult. In the infant, the lower margin of the liver extends inferiorly to a lower level than in the adult, this is an important consideration when making a diagnosis of hepatic enlargement
- Liver pours bile and lipoprotein into Space of Disse

Nase	em Sherzad High-Yield Points	
5'-nucleotidase	The serum activity of elevated in Hepatobiliary disease and this parallel ALP  The 5'-nucleotidase is not altered in bone disease (as in the case with ALP, which increase)	
Prothrombin time	PT is the best indicator of hepatic function synthesis	
Pseudocholinesterase	Produced by the liver and circulating in plasma, deficient in liver failure	

#### **Functions of liver**

- Liver Produces alpha, beta-globin proteins and complement components
- All plasma proteins are formed in the liver, except gamma-globulin which is formed in Reticuloendothelial system, plasma cell and lymphocytes
- The normal liver stores of vitamin K lasts for 1 week
- Liver doesn't produce gamma globulin and interleukin
- Erythropoiesis in middle trimester occurs in the liver
- Prothrombin is synthesized by the liver, a marker of liver function, it decrease in liver disease
- In liver, the billirubin binds to Uridyl glucuronyl transferase
- Microsomal metabolism occur in liver
- Synthesis and secrets bile salt

AND DESCRIPTION OF THE PERSON NAMED IN COLUMN 1

- Secrete insulin-like growth factor I (IGF-I)
- Synthesize cholesterol and release it into the blood
- Except fat, it absorbs all the nutrients from GIT by the portal system
- Most drugs metabolized in the liver
- Ketone bodies increase in the blood as a result of faulty carbohydrate metabolism. They are formed in the liver and consist of acid, acetoacetic acid and acetone

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**GIT Anatomy** 

- The urea cycle (ornithine cycle) takes place in the liver and converts ammonia into urea.
- Liver is Storage site for:
  - √ Glycogen
  - √ Vitamin A
  - ✓ B12

#### Lobes of liver

The division is made by the attachment of the falciform ligament into two anatomical lobes

#### The Large Right lobe

- Right lobe is the largest in volume and contributes to all surface of the liver
- The right lobe is further divided into a quadrate lobe and a caudate lobe by the presence of the gallbladder, the fissure for the ligamentum teres, the inferior vena cava, and the fissure for the ligamentum venosum.
- Quadrate and caudate lobe are anatomical parts of right lob but functional part of the let lob, that's why it is drained by left duct
- Experiments have shown that, in fact, the quadrate and caudate lobes are a functional part of the left lobe of the liver.
- Caudate lobe is situated between inferior venacava and ligamentum venosum, received blood from the left hepatic artery and drains bile into the left hepatic duct
- Quadrate lobe is situated between gall bladder and groove for ligamentum teres, received blood from the right and left hepatic artery and drains into both right and left hepatic dud

#### Small Left lobe

#### Support of liver

- Hepatic vein --- main support --- suspend liver from IVC and have no extrahepatic course
- Peritoneal fold
- Surrounding organs
- The Tone of anterior abdominal wall

#### Zone of liver

#### Zone I: Peripheral zone

NAME AND POST OFFICE ADDRESS OF THE OWNER.

- Affected ist by viral hepatitis
- Richly supplied by blood
- Ingested toxin (cocaine)

#### Zone II: intermediate zone

Affected by yellow fever

### Zone III: Pericentral vein (centrilobular) zone

- Poorly oxygenated and more susceptible to hypoxia, affected ist by ischemia
- It Cytochrome p-450
- Most sensitive to metabolic toxins
- It is the site of alcohol hepatitis

#### Peritoneal Ligaments of liver

#### Falciform Ligament:

- The falciform ligament, which is a two-layered fold of the peritoneum, ascends from the umbilicus to the liver.
- It has a sickle-shaped free margin that contains the ligamentum teres, the remains of the umbilical vein.
- We inject dye to the liver through this ligament teres
- The falciform ligament passes on to the anterior and then the superior surfaces of the liver and then splits into two layers.
- The right layer forms the upper layer of the coronary ligament
- The left layer forms the upper layer of the left triangular ligament.
- The right extremity of the coronary ligament is known as the right triangular ligament of the liver.
- It should be noted that the peritoneal layers forming the coronary ligament are widely separated, leaving an area of liver devoid of peritoneum. Such an area is referred to as a bare area of the liver

#### Coronary Ligament:

- It's a triangular fold of the peritoneum attaching the naked area of the liver to the diaphragm. It includes 2 layers-upper and lower.
- Bare area of the liver is limited by the coronary ligament.
- Attach the liver to the diaphragm. Two peritoneal ligaments are a parts of the coronary ligament
  - ✓ Right triangular ligament: is between the right lobe of the liver and diaphragm
  - ✓ Left triangular ligament: is between the left lobe of liver and diaphragm

#### **Dual blood supply**

- \* Hepatic artery:--Oxygenated blood flow in hepatic artery---25%
- ❖ Portal vein:----Nutrient-rich blood flow through portal vein-75%
- . Liver has the least chance of infarction

NAME AND ADDRESS OF TAXABLE PARTY.

#### Venous drainage and lymphatic drainage

- Venous drainage: The blood drains from the liver through three hepatic veins (right, middle and left) directly into the inferior vena cava.
- . Lymphatic drainage: The liver produces large amount of lymph, about one third to one-half of all body lymph. The lymph vessels leave the liver and enter the several lymph nodes in the porta hepatis. The efferent vessels pass to the celiac nodes. A few vessels pass from the bare area of the liver through the diaphragm to the posterior Mediastinal lymph nodes

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NAME AND ADDRESS OF TAXABLE PARTY.

- Portal vein: Isolated tumor located at Porta hepatis will most likely press branches of the portal vein
- Hepatic artery

#### Histology

- NAME AND ADDRESS OF THE OWN OWN Hepatic lobules-----Structural unit of liver
- A liver sinusoid is a type of capillary known as a sinusoidal capillary, discontinuous capillary or sinusoid, that is similar to a fenestrated capillary, having discontinuous endothelium that serves as a location for mixing of the oxygen-rich blood from the hepatic artery and the nutrient-rich blood from the portal vein
- Ito Cells:
  - Also known as "fat cell" or "stellate cell"
  - o Two major roles:

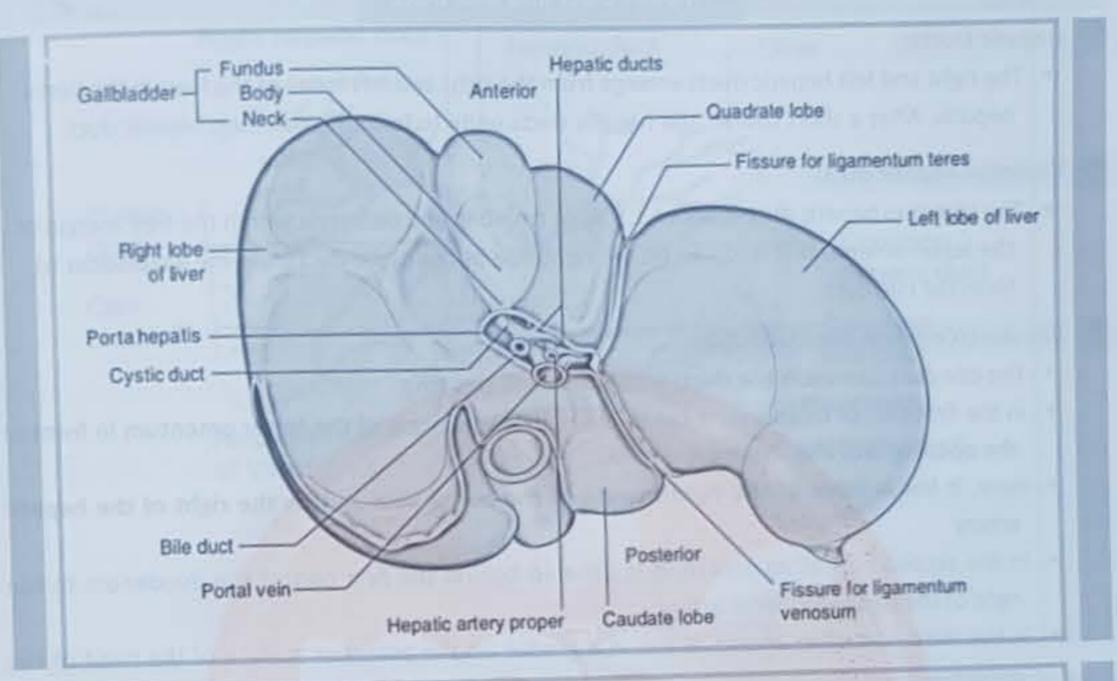
    - ✓ During inflammation or liver damage, produce collagen, i.e. responsible for hepatic fibrosis

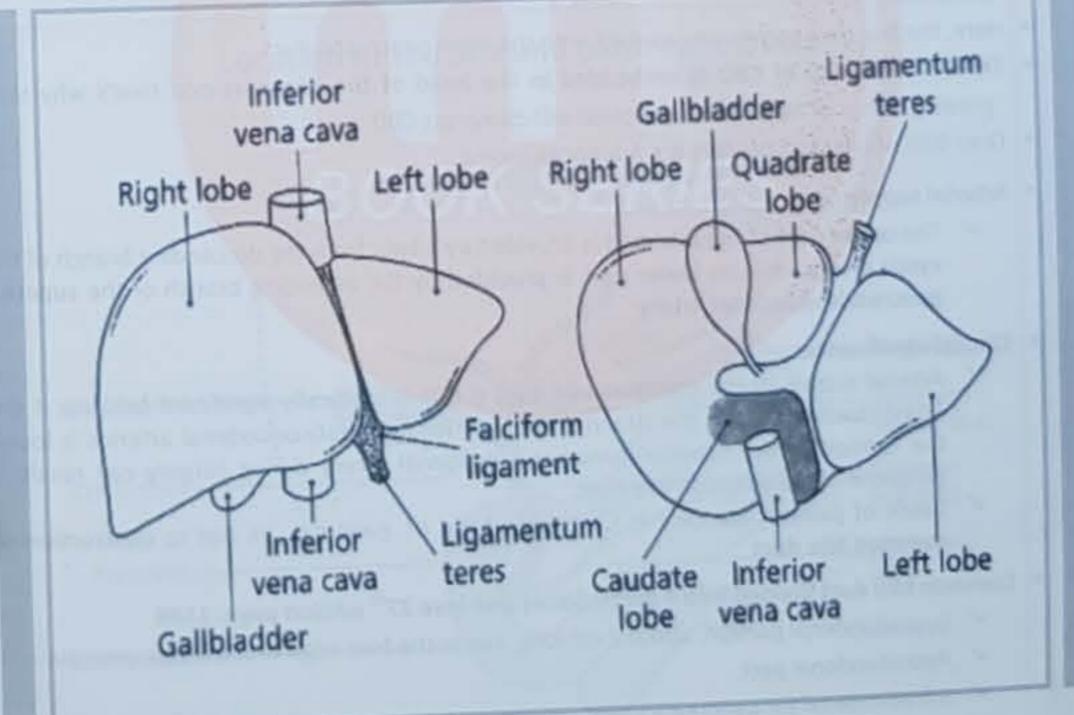
## Naseem Sherzad High-Yield Points

- \* Eating a lot of pizza and burgers will cause Hypertrophy of Steatocytes
- Liver regenerate in 1-2week or 7-10 days by help of Hepatocyte Growth Factor(HGF)
- There are total of 8 surgical lobes. Blood supply distinguishes the surgical lobes by the bifurcation of the right and left hepatic artery and portal vein. The Segmental division depends on portal vein
- A large volume of the liver (80%) can be taken away safely because healthy hepatocyte has great ability of regeneration.
- . The liver is held in position in the upper part of the abdominal cavity by the attachment of the hepatic veins to the inferior vena cava. The peritoneal ligaments and the tone of the abdominal muscles play a minor role in its support. This fact is important surgically because even if the peritoneal ligaments are cut, the liver can be only slightly rotated.
- Cantlie's line: it functionally divides the liver into a right and left liver. It extend between the gallbladder fossa and middle hepatic vein
- Factors precipitating hepatic encephalopathy include drug especially sedative and antidepressant, dehydration (including diuretic, Paracentesis), infection, hypokalemia and
- The liver is the 2nd most common organ injured in abdominal trauma after spleen

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**GIT Anatomy** 





#### Chapter 9 **Hepatic Duct and Bile Duct**



#### Hepatic Ducts:

 The right and left hepatic ducts emerge from the right and left lobes of the liver in the porta hepatis. After a short course, the hepatic ducts unite to form the common hepatic duct

### Common hepatic duct:

■ The common hepatic duct is about 1.5 in. (4 cm) long and descends within the free margin of the lesser omentum. It is joined on the right side by the cystic duct from the gallbladder to form the bile duct

### Bile duct/Common Bile Duct(CBD):

- The bile duct (common bile duct) is about 3 in. (8 cm) long.
- In the first part of its course, it lies in the right free margin of the lesser omentum in front of the opening into the lesser sac
- Here, it lies in front of the right margin of the portal vein and on the right of the hepatic
- In the second part of its course, it is situated behind the first part of the duodenum to the right of the gastroduodenal artery
- In the third part of its course, it lies in a groove on the posterior surface of the head of the pancreas
- Here, the bile duct comes into contact with the main pancreatic duct.
- . The Terminal end of CBD is embedded in the head of the pancreas and that's why slow growing tumor of head of the pancreas will compress CBD
- Over 90% of bile duct cancers are Adenocarcinoma.

#### Arterial supply:

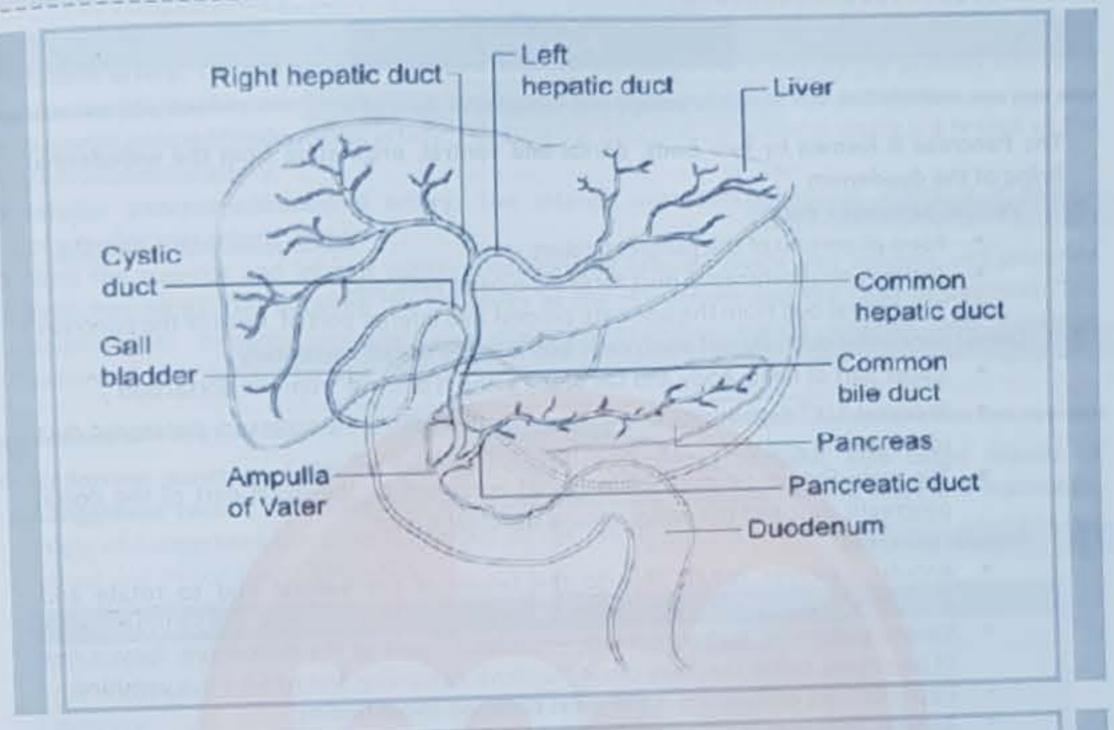
✓ The upper part of the bile duct is provided by a twig from the descending branch of the cystic artery while its lower part is provided by the ascending branch of the superior pancreaticoduodenal artery.

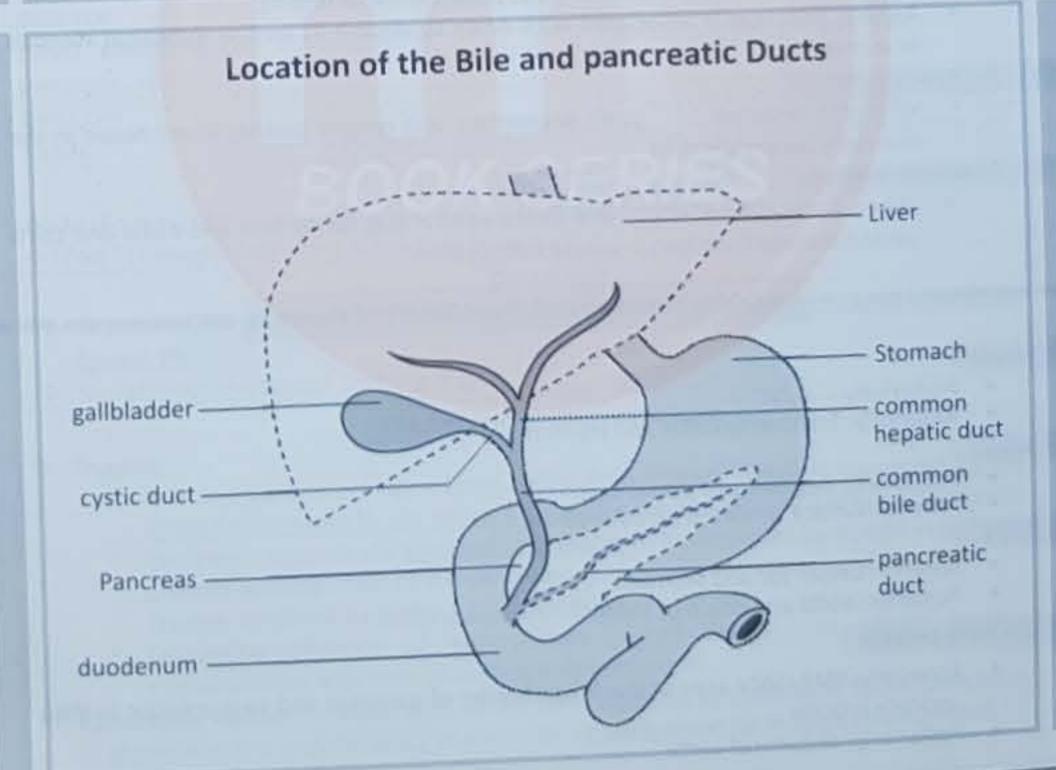
### Clinical significance:

- ✓ Arterial supply of the common bile duct (CBD) is medically significant because if the Anastomosis between the superior and inferior pancreaticoduodenal arteries is lousy, the ligation of the superior pancreaticoduodenal artery during surgery can result in gangrene of the common bile duct.
- ✓ Cause of painless jaundice in Carcinoma head of pancreas is due to obstruction of common bile duct
- Common bile duct divided into 4 parts: Bailey and love 27<sup>th</sup> edition page. 1188
  - ✓ Supraduodenal portion, about 2 cm long, run in the free edge of the lesser omentum
  - ✓ Retroduodenal part
  - ✓ Infraduodenal (or pancreatic) part
  - ✓ Intraduodenal part

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**GIT Anatomy** 





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#### Chapter 9

#### **Pancreas**

## **Embryology and Congenital Anomaly**

The Pancreas is formed by two Buds, dorsal and ventral, originating from the endodermal lining of the duodenum

#### Ventral pancreatic duct:

- Form all portion of the pancreatic duct
- Entire ventral pancreatic duct form main pancreatic duct
- The ventral bud from the uncinate process and inferior part of head of the pancreas

# Dorsal pancreatic duct: Dorsal pancreatic bud is in the dorsal mesentery

- Upper part of head, body and tail of the gland is derived from the dorsal bud
- Proximal 1/3rd degenerate or persist as small channel, the accessory pancreatic duct (of Santorini) and distal 2/3<sup>rd</sup> form main pancreatic duct
- The main Pancreatic duct (of Wirsung) is formed by the distal part of the dorsal pancreatic duct and the entire ventral pancreatic duct

#### Annular pancreas

- Annular pancreas results due to the failure of the ventral bud to rotate and elongates to encircle the upper part of the duodenum.
- Ventral pancreatic bud abnormally encircles 2<sup>nd</sup> part of the duodenum, form a ring of pancreatic tissue that may cause duodenal narrowing and non-bilious vomiting
- Upper GI tract obstruction is the most common initial finding.
- Annular pancreas is associated with down syndrome as well as duodenal stenosis or atresia

#### Accessory pancreas:

 When the proximal 1/3rd don't degenerate and remain persist, it will result in the accessory pancreatic duct

#### Pancreatic divisum

 When distal 2/3<sup>rd</sup> of dorsal and entire ventral bud fail to fuse and distal one third persist thereby form two separate duct system

## Anatomy: Relation and Blood Supply of Pancreas

#### Mead:

- Posteriorly-----IVC
- Anteriorly: Transverse colon and jejunum

#### Meck:

- Posteriorly: Beginning of portal vein
- Anterior surface is related to: pylorus

#### **Body**

- Anterior: Lesser sac and stomach
- Posterior: aorta and origin of SMA

### Uncinate process

- Anteriorly: SMA+SMV arise at the lower border of pancreas and pass anterior to the uncinate process
- Posteriorly: abdominal aorta

#### **Arterial Supply**

- COLUMN TWO IS NOT THE OWNER. . Splenic artery: The splenic artery is the branch of the celiac trunk and it's the primary source of blood supply to the pancreas. Its branches supply the body and tail of the pancreas.
- . Superior pancreaticoduodenal artery: The superior pancreaticoduodenal artery is a branch of the gastroduodenal artery.
- . Inferior pancreaticoduodenal artery: The inferior pancreaticoduodenal artery is a branch of superior mesenteric artery
- . Both the superior and inferior pancreaticoduodenal arteries divide into anterior and posterior branches, which run between the concavity of the duodenum and the head of pancreas. The anastomoses between anterior and posterior branches create anterior and posterior pancreaticoduodenal arterial arcades.

#### Physiology

-. Endocrine pancreas (<5% of the pancreas): islets of Langerhans, also called islands of Langerhans (which are differentiating from pancreatic bud endoderm), secrete 3 hormones. Islets of Langerhans are most numerous in the tail of the pancreas. The human pancreas has about one million islets: ABD---GIS

Type of cell	Associated hormones	Chemical class effect
Alpha cell (2 <sup>nd</sup> most abundant cell )	Glucagon	Increase blood glucose levels
Beta cell (Most abundant cell in pancreas, >60%)	Insulin	Reduces blood glucose levels
	Somatostatin	Inhibits insulin and glucagon release
Delta cell	Pancreatic polypeptide	inhibit the action of the exocrine cel
F-cells	Pancreatic polypeptide	

#### Acinar cell

- . Make most of the weight of pancreas, Secrete NaCl and enzyme
- CCK (through cAMP) and Ach act on acinar cell

#### Ductal cell

- Secrete HCO3 and absorb Cl ---- Pancreatic juice has the highest Ph, gastric acid has lowest Ph
- Secretin act ductal cell and use IP3/Ca

#### The Enzyme of pancreatic juice

#### Trypsin:

- ✓ It is secreted in zymogen form called Trypsinogen, which is converted to the active form trypsin by the enzyme enterokinase and then by itself (autocatalysis),
- ✓ Pancreatic enzyme are <u>secreted in preform</u> to be activated by trypsin in order to prevent autodigestion of the pancreas
- ✓ Trypsin inhibited by Alpha 2 macroglobulin
- ✓ Congenital absence of enterokinase would result in severe protein malabsorption with poor growth and development
- ❖ Pancreatic lipase ——about 80% of the fat is digested by pancreatic lipase, deficiency or absence of this enzyme leads to excretion of undigested fat in feces (steatorrhea)
- Pancreatic amylase

#### Bile Acid

- Daily secretion and Ph of bile: daily secretion: 700-1200ml, Ph: 7.7 to 8.6
- Liver bile: Contain more water (97.6%), contain more HCO3(30 mEq/L) GB bile: Contain less water, more concentrated (89%), contain less HCO3 (10 mEq/L)
- Primary bile acid is formed in hepatocyte from cholesterol (synthesized in the liver)
- Converted to secondary bile acid by bacteria

#### Bile salt

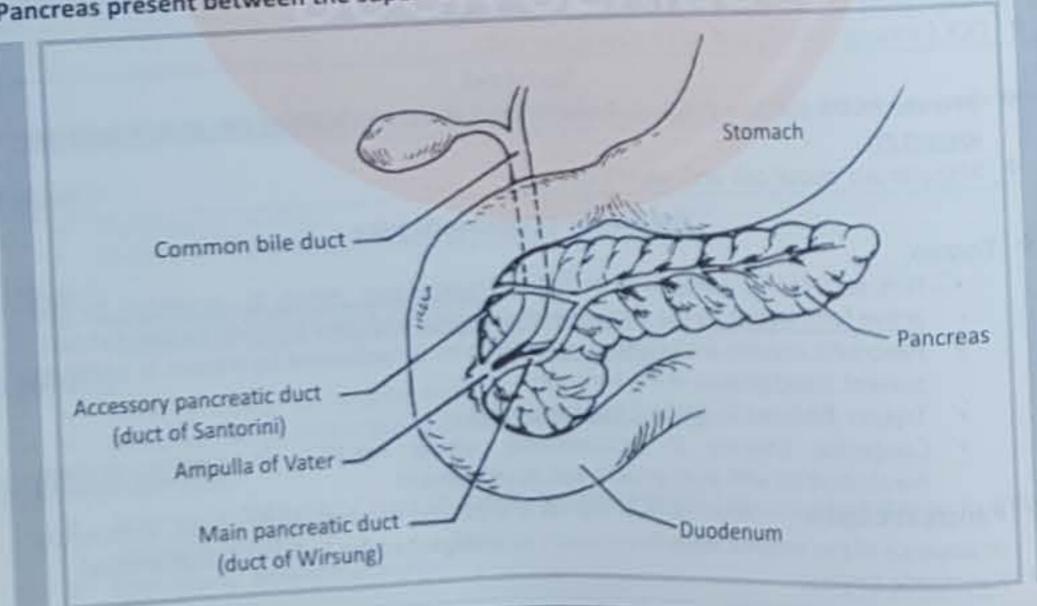
- \* Bile acid conjugated with glycerin or taurine to form their respective bile salts. Include: sodium glycocholate and sodium taurocholate. Daily formation of bile salt: 0.5gm
- Enterohepatic circulation of bile salt: 94% of bile salt are reabsorbed from the small intestine into portal blood → passed to liver → again secreted into portal blood → again reabsorbed and so on; this is called Enterohepatic circulation of bile salts
- . Bile salts are essential for the absorption of fats and fat-soluble vitamin

#### Micelle

- . Bile salt form micelle, containing Fatty acid, monoglycerides, fat-soluble vitamins and cholesterol
- . In bile salt deficiency, micelle not formed, which produces a fatty stool

#### Clinical Significance

- . Carcinoma of the head of the pancreas is common. It compresses the bile duct resulting in consistent obstructive jaundice. It might press the portal vein or may include the stomach because of the shut area of these structures to the head of pancreas.
- Since the pancreas grows at the junction of the foregut and midgut, it's furnished by the branches of the artery of foregut (coeliac trunk) and the branches of the artery of the midgut (superior
- ❖ Pancreas present between the superior mesenteric artery and celiac trunk or between T12-L1



Chapter 9

Spleen

- Iramunoglobulin synthesis occurs in the spleen
- Immunoglobulin synthesis occurs by plasma cell
- Largest lymphoid organ of the body
- Simple squamous epithelium (Peritoneum) covers the capsules of the spleen
- Splenic infarction occurs in CML
- Streptococcus pneumonia or Pneumococcus is the most common cause of sepsis in Asplenic patient
- The spleen typically weighs 150 grams in a typical adult and spans about 11 cm (4.3 inches) vertically in its longest dimension. The Spleen is most amenable organ to spontaneous rupture.
- Spleen injury occur if 9th and 10th ribs fractured
- Spleen arise from dorsal mesogastrium, so mesodermal in origin
- Spleen is the least common site for malignancy
- \* Heme is converted to Bilirubin by macrophage in Reticuloendothelial cell like spleen
- \* Wandering spleen is a rare condition in which there is complete absence or weakness of ligament that hold the spleen in anatomical position
- Accessory spleen if present found in the tail of the pancreas
- There is no cortex or medulla in spleen

#### White pulp of spleen:

- ✓ Consist of lymphoid tissue that surrounds branches of splenic artery and includes Priarterial lymphatic sheath (PALS) and lymphoid nodules(splenic nodules or malpighian bodies)
- ✓ Thick sleeves of lymphoid tissue that provides the immune function of the spleen
- ✓ Sago spleen, amyloid deposit involves walls of arterioles of white pulp and replace the follicle
- √ Function:
  - o Rich in lymphocyte
  - o The White pulp of the spleen has a very important role in the normal immune response to infection
  - Lymphoid follicles, rich in naïve B-lymphocyte

### Marginal zone of spleen:

- ✓ It is the sinusoidal region between white pulp and red pulp at the periphery of PALS.
- ✓ It is the first site where blood contact the splenic parenchyma
- Antigen presentation take place in the marginal zone

### Red pulp of Spleen:

- ✓ The red pulp makes up roughly 80% of the spleen parenchyma ✓ The red pulp is Composed of the venous sinus (sinusoids) and cellular cords called splenic
- ✓ The splenic cords are lined by macrophages and function as sieve through which blood in
- Lardaceous spleen, amyloid involves the wall of splenic sinuses and connective tissue in the red pulp
- Function:
- Removes aged/old/dead defective RBCs along with antigen and microorganisms
  - Store breakdown products of RBCs
  - Storage of up to 1/3 of body platelets supply, sequestrations of platelets
  - o Rich in macrophages
  - Phagocytosis of opsonised bacteria by macrophages
  - Storage of RBCs, in case of hypovolemia these can be released following any injury resulting in blood loss

#### E Ligament:

- Phrenicocolic ligament:
  - Prevent downward displacement of spleen
- Gastrosplenic ligament:
  - Extend from hilum of spleen to greater curvature of stomach
  - Contain: short gastric artery and left gastroepiploic artery
- ✓ Splenorenal ligament (or lienorenal ligament)
  - Carry splenic vessel and tail of pancreas

## Naseem Sherzad High-Yield Points

- . Howell-Jolly bodies are Histopathological finding of basophilic nuclear remnants (cluster of DNA) in circulating erythrocytes.
- Howell jolly bodies are normally removed from RBC's by splenic macrophages.
- . Howell jolly bodies are present in Severe anemia, Patient without spleen and Sickle cell anemia (because in sickle cell anemia Auto splenectomy occur)
- \* Target cell, present in postsplenectomy patient
- Thrombocytosis (increase in Platelet count) is seen after splenectomy and this the first effect seen after splenectomy followed by Howell jolly body.
- Massive splenomegaly: Mnemonic HMC: CML, Myelofibrosis + Malaria and Hairy cell
- Auto-splenectomy is occurring in sickle cell anemia and celiac disease.
- Gandy-Gamna nodules or gandy-gamn bodies sometimes known as Gamna-Gandy nodules or Gamna-gandy bodies, are small yellow-brown, brown or rust-colored foci found in the spleen in patient with splenomegaly due to portal hypertension as well as sickle cell disease Hematological indication for splenectomy: Spherocytosis, ITP and Hypersplenism

#### Gall Bladder



**GIT Anatomy** 

- . Location: The gallbladder is a pear-shaped sac lies on the undersurface of the liver in the main liver scissure at the junction of the right and left of the liver.
- . Physiology: It has a capacity of 30 to 50mL and stores bile, which it concentrates by absorbing water. The liver excretes bile at a rate estimated to be approximately 40mL/hour. About 95% of bile salt are reabsorbed in the terminal ileum(Enterohepatic circulation)
- . Histology: The mucosa is composed of a simple columnar epithelium and a richly vascularized lamina propria. The wall of the bladder does not have a muscularis mucosa and submucosa. When the gallbladder is empty, the mucosa thrown into highly convoluted folds. It has a muscular wall whose contraction, stimulated by CCK, force bile from its lumen into the duodenum
- . Blood supply: Gall bladder is supplied by cystic artery only
- . Lymphatics: The lymphatic vessels of the gallbladder (subserosal and submucosal) drain into the cystic lymph node of lund. From these nodes lymph pass to the celiac group of preaortic nodes
- . Nerve supply: The gallbladder gets its nerve supply via cystic plexus created by the sympathetic fibers (T7 T9), parasympathetic fibers (right and left vagus nerve) and fibers of the right phrenic nerve

### Pathology high yield:

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- ✓ Strawberry Gall bladder occurs due to increased cholesterol deposition.
- ✓ The most common type of gallbladder cancer is Adenocarcinoma

#### Hartmann's pouch:

- ✓ Hartman pouch is an out-pouching of the wall of the gallbladder at the junction of the neck of the gallbladder and the cystic duct
- ✓ This Is not the feature of the normal gallbladder and is always associated with the pathological condition
- ✓ It is the commonest site for impaction of gallstones

### Calot's triangle or the hepatobiliary triangle:

- ✓ The space bounded by the cystic ducts inferiorly, the common hepatic duct medially and the superior border of the cystic artery.
- ✓ It is an important surgical landmark as the cystic artery usually can be found within its boundaries and should be identified by the surgeon performing a cholecystectomy to avoid damage to the extrahepatic Billary system

#### Function:

- ✓ The main function of the gallbladder is to store the bile secreted by the liver and then deliver it into the intestine for digestion and absorption of fat
- ✓ The epithelial cells activity absorbs water and solutes and concentrate it
- ✓ Selectively absorb bile salts, keeps the bile acid, Excrete cholesterol

# **Arterial System**

## **Abdominal Aorta Branches**



- ❖ Inferior phrenic arteries: All these are the first branches of the abdominal aorta and originate
- Three anterior visceral branches (Single/unpaired): The celiac artery, superior mesenteric artery
- . Three lateral visceral branches (Paired): The suprarenal artery, renal artery, and testicular or
- Five lateral abdominal wall branches(Paired): The inferior phrenic artery and four lumbar arteries
- . Three terminal branches: The two common iliac arteries and the median sacral artery
- Mariant features:
  - ✓ Abdominal Aorta is the main blood vessel in the abdominal cavity.
  - ✓ It is the largest blood vessel in the abdomen opposite to the lower border of the T12 vertebra or intervertebral disc between vertebrae T12 and L1 that starts as the continuance of descending thoracic aorta in the aortic orifice of the diaphragm is known as the abdominal aorta.
  - ✓ It descends vertically downward and somewhat to the left, in front of the vertebral column, and ends in front of the lower part of the body of L4 vertebra (about 1.25 cm) to the left of the median plane by splitting into left and right common iliac arteries.
  - It keeps on diminishing in size rapidly due to the use of many large branches.
  - ✓ Due to its dependence on the bodies of the vertebrae, it has a convex forward curve.
  - The summit of its convexity corresponds to the third lumbar vertebra.
  - ✓ At the level of the transverse colon SMA supply converted into IMA supply.

#### Celiac Trunk --- LCS



- 1) Left gastric artery: -----It supplies the lower third of the esophagus and the upper right part of the stomach. It is the smallest branch
- 2) Common Hepatic artery: Branches
  - Right gastric artery: It supplies the lower right part of the stomach.
  - Gastroduodenal artery: branches
    - ✓ Right gastroepiploic artery: Supplies the stomach along the lower part of the greater curvature.
    - ✓ Superior pancreaticoduodenal artery
  - Terminal branches
    - -gives cystic artery which supplies gallbladder and ✓ Right hepatic artery-----
    - ✓ Left hepatic artery
  - Variations:
    - ✓ Replaced right hepatic artery = arises from the SMA (20%)
    - ✓ Replaced left hepatic artery = arises from the left gastric artery (15%)

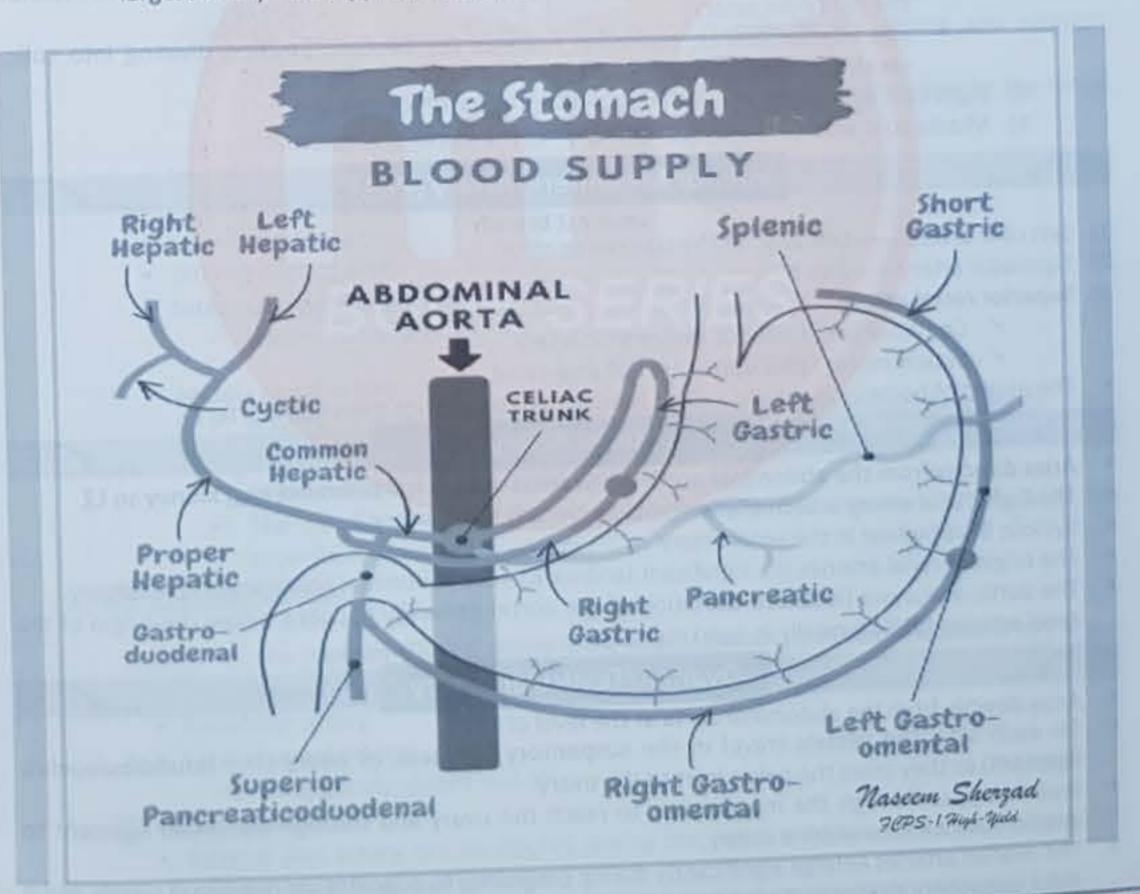
### 3) Splenic artery:

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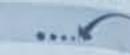
- · Largest branch of the celiac trunk
- The splenic artery is the branch of the coeliac trunk and it's the primary source of blood supply to the pancreas.
- Its branches supply the body and tail of the pancreas.
- Two branches are called. 1 large branch which originates near the tail and runs toward the neck is known as arteria pancreatica Magna. Another comparatively small branch, which runs toward the tip of the tail, is referred to as arteria caudae pancreatica.

#### Branches:

- Short gastric artery: Supply the fundus. Short gastric artery having poor Anastomosis and would most likely affected by pressure on the splenic artery
- Left gastroepiploic artery: Supply the stomach along the upper part of the greater curvature
- Greater pancreatic artery (great pancreatic artery or arteria pancreatica Magna), is the largest artery that supplies the pancreas. It arises from the splenic artery.



# Superior Mesenteric Artery (SMA)



- Abdominal angina occur due to obstruction of SMA
- Superior and inferior mesenteric artery are joined by marginal artery
- Superior and inferior mesenteric artery overlap at the splenic flexure.
- . The splenic flexure is a watershed region as it receives dual blood supply from the terminal branches of the superior mesenteric artery and the inferior mesenteric artery, thus making it prone to ischemic damage in cases of low blood pressure because it does not have its own primary source of blood. Splenic flexure is the most common site of ischemic colitis
- Relations: it is crossed anteriorly by the splenic vein and the neck of the pancreas, posterior to the SMA are the left renal vein, the uncinate process and the 3rd part of the duodenum
- Branches
- 1) Inferior pancreaticoduodenal artery—Ist branch, Supplies head of the pancreas, ascending and inferior part of the duodenum
  - 2) Jejunal and ileal artery
  - 3) Ileocolic artery: This passes downward and to the right towards the right iliac fossa where it divides into superior and inferior branches:
    - The superior branch passes upward along the ascending colon to anastomoses with the right colic artery;
    - . The inferior branch continues towards the ileocolic junction dividing into colic, cecal, appendicular, and ileal branches
  - 4) Right colic artery
  - 5) Middle colic artery-----up to right 2/3<sup>rd</sup> of the transverse colon

### Inferior Mesenteric Artery (IMA)

#### Smallest branch

- Left colic artery——Left 1/3<sup>rd</sup> of the transverse colon
- Sigmiodal artery----2 or 3
- 3) Superior rectal artery
  - ✓ Continuation of inferior mesenteric artery
  - ✓ Supply rectum plus upper 1/3<sup>rd</sup> of anal canal.
- The ascent of horseshoe shaped kidney is prevented by inferior mesenteric artery

#### Renal Artery

- Arise directly from the abdominal aorta at the level of L2— to remember two kidney so L2
- The Right renal artery is normally longer than the left renal artery
- Systolic BP is highest in the renal artery
- The origin of renal arteries is a significant landmark in the abdominal aortic aneurysm surgery.
- The aortic aneurysm (localized dilatation of the aorta) generally happens below the origin of the renal arteries (95%) typically in aged men.

### Ovarian/Testicular Artery

- Arise directly from the abdominal aorta at the level of L2
- On each side, the vessels travel in the suspensory ligament of ovary (the infundibulopelvic ligament) as they cross the pelvic inlet to the ovary
- Branches pass through the mesovarium to reach the ovary and through the broad ligament to anastomose with the uterine artery.
- anastomose with the decrine and it anastomose with the decrine blood supply and it.

  The ovarian arteries enlarge significantly during pregnancy to augment uterine blood supply and it. most commonly damages during hysterectomy at the level of the pelvic brim

# Chapter 9

**GIT Anatomy** 

### Common iliac artery and Median Sacral Artery

- The right and left common iliac arteries are the terminal branches of the aorta.
- They arise at the level of the fourth lumbar vertebra and run downward and laterally along the medial border of the psoas muscle.
- Each artery ends in front of the sacroiliac joint by dividing into the external and internal iliac arteries.
- At the bifurcation, the common iliac artery on each side is crossed anteriorly by the ureter
- 1) Internal iliac artery:

.....

#### Anterior division:

- Umbilical artery---This is the first branch of the anterior trunk
  - ✓ Branch: Superior vesical artery
- Uterine artery:
  - Lies between peritoneum and ureter
  - Commonly injured during C-section
  - ✓ Pass in front of the ureter to supply the uterus
  - ✓ Courses medially and anteriorly in the base of the broad ligament to reach the cervix
  - ✓ The uterine artery is the major blood supply to the uterus and enlarges. significantly during pregnancy
  - ✓ Through anastomoses with other arteries, the vessel contributes to the blood. supply of the ovary and vagina as well.
- Vaginal artery
- Obturator artery
- Inferior vesical artery
- Inferior Gluteal artery
- Internal pudendal artery:
  - ✓ Inferior rectal artery

#### Middle rectal artery

- ✓ It Remains in true pelvis and cross from medial to lateral side of the pelvis
- ✓ It enters downward and medially via the lateral ligament of the rectum and supplies the lower part of the rectum.
- ✓ The middle rectal arteries are unimportant because they supply only the superficial layers of the rectum.

#### Posterior division

- Superior Gluteal artery
  - ✓ The superior Gluteal artery is the largest branch of the internal iliac artery and is the terminal continuation of the posterior trunk
- Iliolumbar artery
- Lateral sacral artery:
  - ✓ Congenitally absent in 0.5%

#### Clinical pearls:

 Internal iliac artery can be injured during the removal of ovaries (oophorectomy) or ovarian mass from ovarian fossa

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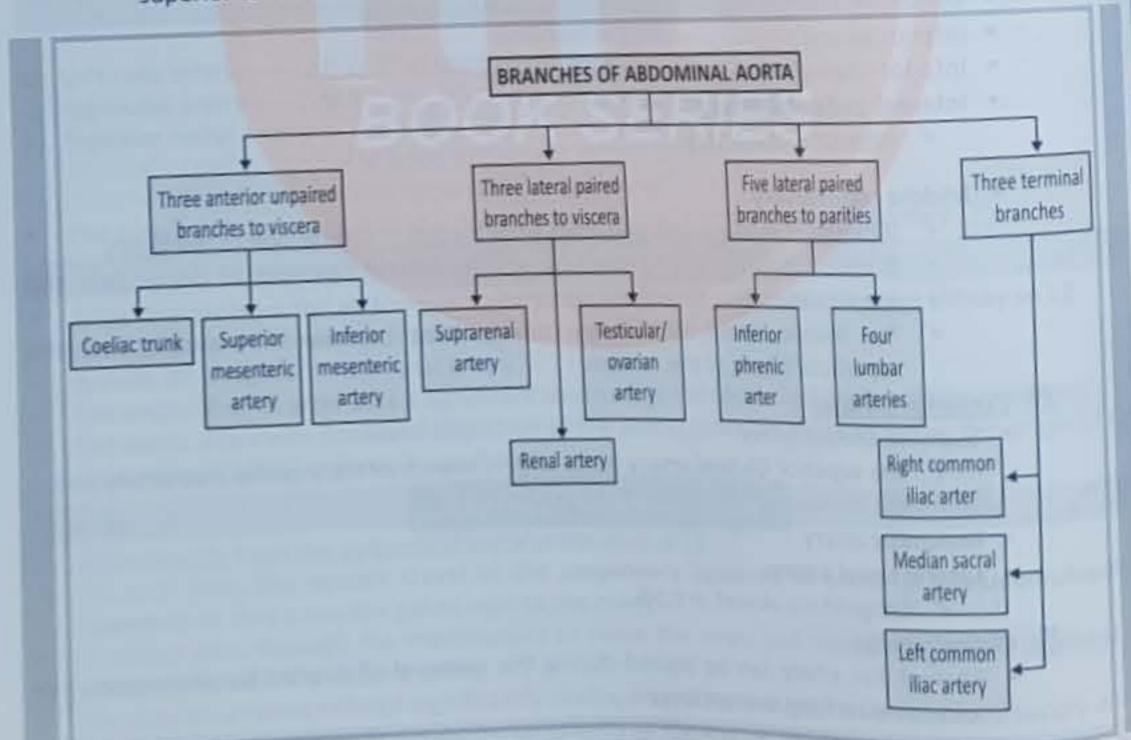
#### Chapter 9

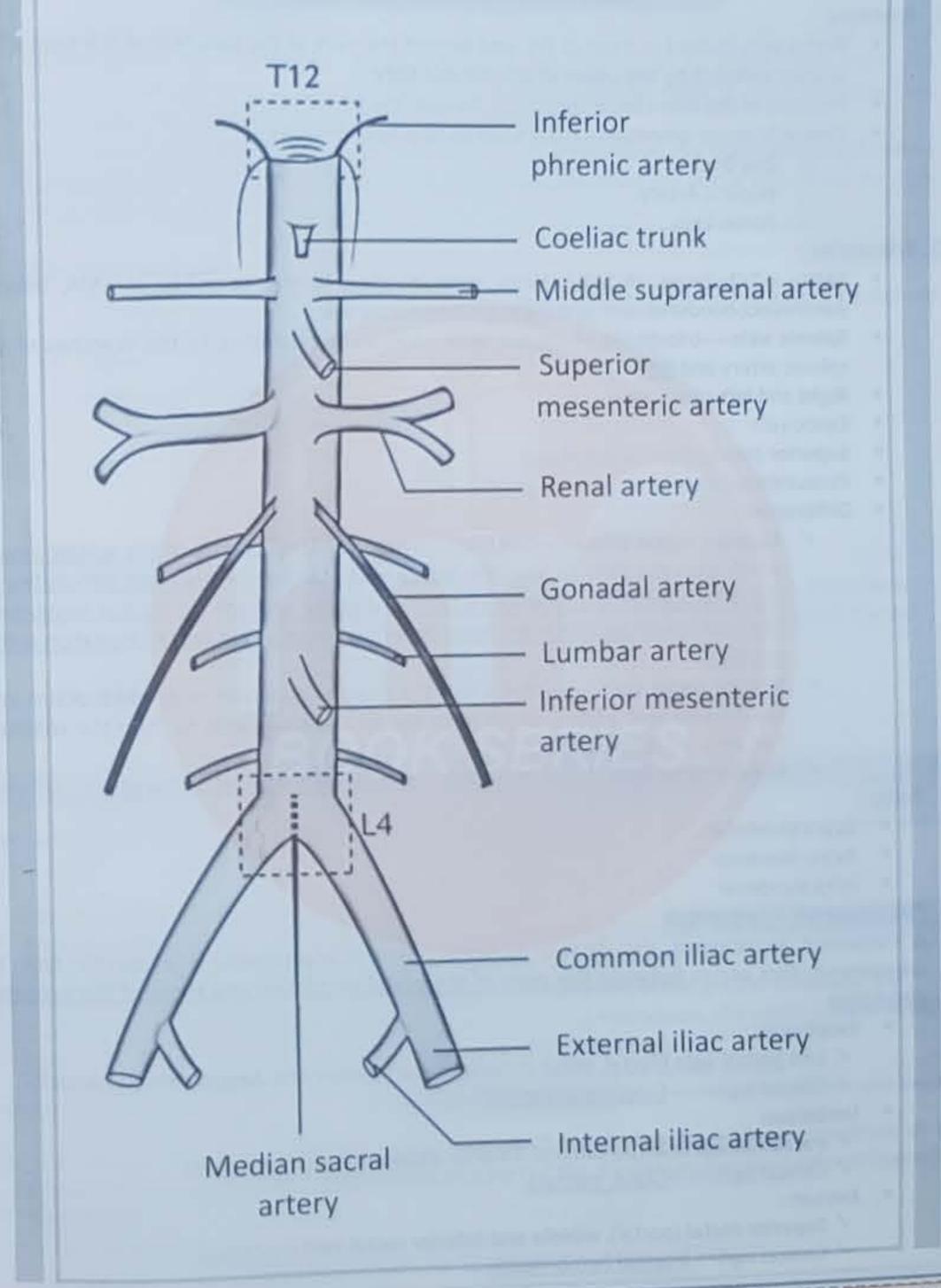
#### 2) External iliac artery

- Inferior epigastric artery
- ✓ The inferior epigastric artery moves upwards around the medial side of the deep inguinal ring. The terminal branches of the inferior epigastric artery then anastomose with the superior epigastric artery, a blood vessel that is a continuation of the internal
  - Inferior epigastric artery enters the rectus sheath, and is a landmark to differentiate between direct and indirect inguinal hernia.
  - ✓ The lateral end of Hesselbach's inguinal triangle, a crucial landmark in laparoscopic inguinal hernia repair is created by inferior epigastric artery
  - ✓ Commonly injured in <u>suprapubic incision</u>
  - ✓ Branches:
    - Accessory obturator artery
    - o Cremasteric artery
  - Deep circumflex iliac artery
  - Femoral artery:
    - ✓ It is the Terminal branch/It is a continuation of the external iliac artery
    - ✓ When the external iliac artery passes posterior to the inguinal ligament, its name. changes to femoral artery,

#### 3) Median Sacral Artery:

 The median sacral artery originates from the posterior surface of the abdominal aorta just superior to the aortic bifurcation at vertebral level L4 in the abdomen.





#### 1) Anatomy

Portal vein formed in front of IVC and behind the neck of the pancreas at the level of 2<sup>rd</sup>

**Portal Vein** 

- lumbar vertebra by the union of splenic and SMV Pressure in the liver can be measured through the portal vein
- Course in lesser omentum—from anterior to posterior –DAV
  - o Bile Duct
  - Hepatic Artery
  - o Portal Vein

#### 2) Tributaries

- SMV:—Tributaries of SMV—Veins corresponding to the branches of SMA, Inferior pancreaticoduodenal vein and Right gastroepiploic vein
- Splenic vein—tributaries of splenic vein—Veins corresponding to the branches of the splenic artery and IMV
- Right and left gastric vein
- Cystic vein
- Superior pancreaticoduodenal vein
- Paraumbilical vein
- Differences:
- ✓ Superior rectal vein——continues upward as IMV—open into the splenic vein which joins the SMV to form the portal vein. The hemorrhoids are varicosities of the tributaries of the superior rectal vein and are covered by mucous membrane, The superior rectal vein is the most dependent part of the portal circulation and is
  - Inferior rectal vein------drains into the internal pudendal vein, which drains into the internal iliac vein----which joins the external iliac vein to form the common iliac vein-----forming IVC
  - ✓ Middle rectal vein: drains into the anterior division of internal iliac vein

#### 3) Parts:

- Supra duodenal
- Retro duodenal
- Infra duodenal

## 4) Portosystemic Anastomosis

A Portacaval anastomosis also known as porto-systemic anastomosis is a specific type of anastomoses that occurs between the veins of the portal circulation and those of the systemic circulation

- Esophagus:
- ✓ Left gastric vein (Portal, dilate in portal hypertension) and Azygos vein (systemic)
  - ✓ Clinical sign-----Esophageal varices
- Umbilicus:
  - ✓ Paraumbilical vein (portal) and Anterior abdominal vein (systemic)
  - ✓ Clinical sign-----Caput medusa
- Rectum:
- ✓ Superior rectal (portal), middle and inferior rectal vein (systemic)
  - ✓ Clinical sign—Internal hemorrhoids

### Chapter 9

**GIT Anatomy** 

### Naseem Sherzad High-Yield Points

- \* Vasoactive agent: Terlipressin is currently the only licensed vasoactive agent and is supported by NICE guideline. It has shown to be of benefits in initial hemostasis and preventing re-bleeding. Octreotide may also be used although there is some evidence that Terlipressin has a greater effect on reducing mortality
- If the celiac trunk is compressed by some space-occupying lesion the organ which will not be ischemic is liver, because the liver also gets blood supply from the portal vein which has 70% oxygenated blood

#### 5) Portal hypertension:

- as portal vein Hypertension
- Increase in portal diameter occur after portal hypertension
- Post hepatic causes:
  - ✓ Hepatic vein obstruction (Budd-Chiari syndrome)
  - ✓ Inferior vena cava obstruction
  - ✓ CCF
  - ✓ Tricuspid regurgitation
  - Pericardial effusion and constrictive pericarditis

#### Hepatic causes:

- ✓ Pre-sinusoidal: portal tract fibrosis or infiltration, Schistosomiasis, Sarcoidosis
- Sinusoidal: liver cirrhosis, polycystic liver disease, metastatic malignant disease
- Post-sinusoidal: veno-occlusive disease of liver

#### Pre-hepatic causes:

- Obstruction of portal vein
- Obstruction of splenic vein

#### Sac, Pouches and Hiatus



#### **Omental Bursa**

#### (Lesser sac)

- Lies behind the stomach and lesser omentum
- Anterior wall, from above downward, by the caudate lobe of the liver, the lesser omentum, back of the stomach and the anterior two layers of the greater omentum
- Posterior wall, from below upward by the posterior two layers of the greater omentum the transverse colon and the ascending layer of the transverse mesocolon, the upper surface of the pancreas the left suprarenal gland the upper end of the left kidney

#### Lesser Omentum

- NAME AND ADDRESS OF THE OWNER, WHEN It is the double layer of peritoneum that extends from the liver to the lesser curvature of the stomach (hepatogastric ligament) and the first part of the duodenum (hepatoduodenal ligament).
- \* Attachment:
  - Superiorly:
    - ✓ Porta hepatis and fissure for ligamentum venosum of liver

- Inferiorly:
- ✓ Lesser curvature of stomach and first (superior) part of the duodenum

### Hepatogastric ligament

- it connects the liver to the lesser curvature of the stomach
- It contains the right and the left gastric arteries.

### Hepatoduodenal ligament:

- It is the portion of the lesser omentum extending between the porta-hepatis of
- the liver and the superior part of the duodenum. Running inside it are the following structures collectively known as the portal triad: BPH
  - ✓ Bile duct (lies laterally)

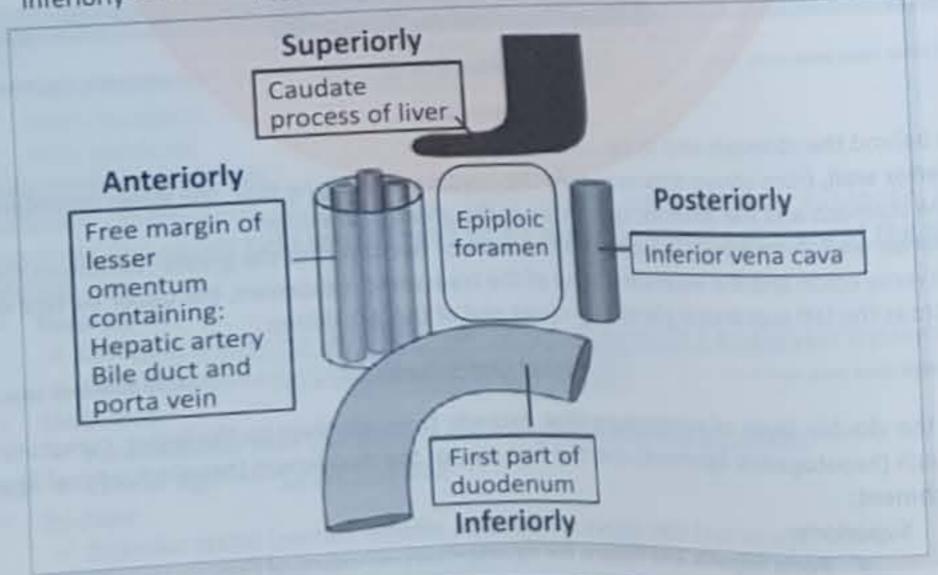
  - ✓ Hepatic artery (lies medially) and Hepatic plexus (The hepatic plexus, the largest) offset from the celiac plexus, receives filaments from the left vagus and right phrenic nerves.)
- Manual compression of the hepatoduodenal ligament (cause compression of portal Hepatis: CBD, hepatic artery and portal vein are the structure of porta hepatis) during surgery is known as the Pringle's Maneuver.
- The Hepatic vein is not the content of the lesser omentum

## Epiploic foramen or foramen of Winslow

It is the passage between the lesser and greater sac

#### Boundaries:

- -Free border of the lesser omentum Anteriorly—
- -Inferior vena cava (IVC) Posteriorly —
- -Caudate process of the caudate lobe of the liver Superiorly -
- First part of the duodenum Inferiorly—



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**GIT Anatomy** 

#### Hepatorenal (Morison's) Pouch

- Most dependant (gravitationally) part of the peritoneal cavity in the supine position
- **Boundaries**:
  - Anterior: Right lobe of liver, gallbladder
  - Posteriorly: Second part of the duodenum, right flexure of the colon, head of the pancreas
  - · Superior: Inferior layer of the coronary ligament
  - . Inferiorly: Opens to the general peritoneal cavity

#### Referred Pain

1) Gall bladder

- Phrenic nerve-----C345
- 2) Shoulder pain referred from pleura
  - Phrenic nerve-----C345
- 3) Epigastrium:
  - Greater splanchnic nerve(T5-9)
- 4) Jejunum
  - Greater and lesser splanchnic nerves
- 5) Umbilicus:
  - lesser splanchnic nerve (T10-11)
  - Dermatome-----T10
- 6) Ovarian:
  - Obturator nerve
- 7) Ureteric pain to groin region:
  - · Genitofemoral nerve
- 8) Renal colic pain in loin by:
  - Ilioinguinal nerve
- 9) Appendix:
  - T-10
- 10) Intermittent pain of small intestine felt in
  - Umbilical region
- 11) Pain on defecation:
  - · Pudendal nerve
- 12) Patient with Ca- rectum develops pains on the posterior aspect of the thigh, nerve responsible
  - Sacral nerve
- 13) Biliary colic:
  - Referred pain is felt in the right upper or the epigastrium (T7,8,9 dermatome)
- 14) Angina pectoris
  - Thoracic splanchnic nerve (T1-T5)

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#### Chapter 9

## 15) Peritoneal diaphragm pain radiate to

· Neck and shoulder

### 16) Anorectal incontinence:

 Stretching of the pudendal nerve during a traumatic child birth can result in pudendal nerve damage and anorectal incontinence

Organs	Nerve supply Spinal cord	Clinical Example
	Anterior and posterior vagal trunk, presynaptic sympathetic fiber reach celiac and other ganglia through greater splanchnic	
Duodenum	Vagus nerve. Presynaptic sympathetic fibers reach celiac and superior mesenteric ganglia through greater splanchnic nerve	perforate
Small intestine (jejunum and ileum)	Posterior vagal trunk.  Presynaptic sympathetic fibers reach celiac ganglion through greater splanchnic nerve	
Spleen	Celiac plexus, especially from greater splanchnic T6-T nerve	infarct)
Gallbladder and live	Nerve are derived from celiac plexus (sympathetic), vagus nerve (parasympathetic) and right phrenic nerve	Epigastric region and later to right hypochondriac region
Kidney/ureters	Nerve arises from the renal plexus and consist of sympathetic, parasympathetic and visceral afferent fiber from thoracic and lumbar splanchnic and the vagus nerve	Small of back, fland extending to the groin

Reference: Clinical orientated anatomy, 4th edition, Page 234

#### Landmark and Clinical Points

#### Inferior Vena Cava (IVC)

- The inferior vena cava is the largest vein in the human body, the great saphenous vein is the longest vein in the human body
- Inferior vena cava is located to the right of the midline
- . The inferior vena cava begins as the left and right common iliac veins unite at about the level of L5. It passes through the thoracic diaphragm at the caval opening at the level of T8.----Remember the digit 58 (starts at L5, ends at T8)
- Right-sided veins(Testicular/Ovarian and Suprarenal veins) drain directly into IVC because IVC is on right side
- ❖ Left-sided veins(Testicular/Ovarian and Suprarenal veins) first drain into the left renal vein which passes in front of the aorta to drain into IVC
- . Importantly, the longer left renal vein crosses the midline anterior to the abdominal aorta and posterior to the superior mesenteric artery and can be compressed by an aneurysm in either of these two vessels
- Inferior vena cava is primarily a right-sided structure, unconscious pregnant women should be turned on to their left side (the recovery position), to relieve pressure on it and facilitate venous return
- Surgical Consideration: Any surgical procedure involving the thoracic cavity or abdomen requires attention to the location, condition, and orientation of the inferior vena cava in relation to other structures and organs. Injury to the IVC can result in significant blood loss if not corrected promptly.
- . If the inferior vena cava becomes blocked, the ascending lumbar veins become important collateral channels between the lower and upper part of the body

#### Tributaries:

- Right renal vein, right suprarenal vein and right testicular/ovarian vein drain directly into IVC
- Left suprarenal/adrenal vein and left testicular/ovarian first drain into the left renal vein and then left renal vein open directly into the IVC
- Inferior phrenic vein and four lumbar veins
- Two common iliac vein (external iliac and internal iliac vein) and median sacral vein
- Two Hepatic veins

Aorta

- ❖ Abdominal aorta begins at T12 and ends at L4 with its bifurcation into the common iliac arteries. -----remember the digit 12-4(starts at T12, ends at L4)
- On its right side lie the inferior vena cava, the cisterna chyli, and the beginning of the Azygos vein. On its left side lies the left sympathetic trunk.
- Right ovarian/testicular artery arises from the aorta, and the aorta is on the left side so the right ovarian/testicular artery will pass in front /anterior to IVC to lie on the right side of IVC.

## Herniotomy: Structures at Risk

- --- Inferior epigastric artery \* Artery----
- Nerve---ilioinguinal nerve
- Division of ilioinguinal nerve during appendectomy lead to direct hernia
- Common structure encountered during normal inguinal repair is Pampinifrom plexus

### Appendectomy: Structures at Risk

- ------Deep circumflex artery · Artery-
- \* Nerve or mention structure------Iliohypogastric nerve

### **Erection, Emission and Ejaculation**

- ----Parasympathetic (Pelvic nerve) · Erection----
- Sympathetic (Hypogastric nerve) · Emission----
- \* Ejaculation-Pudendal nerve (Visceral plus somatic)
- · Female sexual stimulation ------Parasympathetic

### Structures along Transpyloric plane

Please Feed Him Some Love

- Pylorus---lower border of L1
- Fundus of gallbladder
- Hilum of kidney
- SMA origin
- Lower border of spinal cord

#### Facts about 250

- ✓ O₂ required for 70 kg in GA----250 mm Hg
- ✓ The Total surface area of GIT is 350m² but only 250m² is absorptive
- ✓ Absolute refractive periods of the heart is 250 mSec

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**GIT Anatomy** 

## The Spread of Infection and Placement of Tubes

- Acute pancreatitis and posterior duodenal perforation
  - Lesser sac

D B B F

- **Appendicitis** 
  - Subphrenic space
- Anterior duodenal perforation
  - Via right paracolic gutter and thus down to Right Iliac Fossa (RIF)
  - The differential diagnosis between perforated duodenal ulcer and a perforated appendix may be difficult
- After Cholecystectomy, surgeon places drain in:
  - Right subhepatic space
- Laparotomy
  - Right paracolic gutter
- Ruptured ectopic pregnancy
  - Rectouterine pouch or pouch of Douglas

### Retroperitoneal structures

#### SAD PUCKER

- Suprarenal gland
- Aorta and IVC
- Duodenum---all except the first 2cm
- Pancreas----except the tall
- Colon-----ascending and descending
- Kidney
- Esophagus-----lower 2/3<sup>rd</sup>
- Rectum------Partially

## Number of layers crossed when a cannula is inserted in different body region

- Abdomen (midline): 7 layers
- Abdomen (flank region): 9 layers
- Scrotum: 7 layers
- In spinal tap: 8 layers
- Thorax: 8 layers (if Endothoracic fascia and partial pleura are taken as a single layer then 7 layers are crossed

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#### **Embryology**

### 1) Dorsal mesogastrium derivatives

- Greater omentum (The greater omentum is often referred to by the surgeons as the abdominal policeman)
- Gastrosplenic ligament
- Gastrophrenic ligament
- Lienorenal ligament

### 2) Ventral mesogastrium derivatives

- Lesser omentum (connects with duodenum)
- Falciform ligament
- Coronary ligament
- Right and left triangular ligament

### 3) Buccopharyngeal membrane:

- It separate the stomodium from the foregut
- Buccopharyngeal membrane rupture at the end of the third week

### 4) Buccopharyngeal fascia:

 Parallel to the carotid sheath and along its medial aspect the prevertebral fascia gives off a thin lamina, the buccopharyngeal fascia, which closely invests the Constrictor muscles of the pharynx, and is continued forward from the superior Constrictor on to the Buccinator.

#### 5) Cloacal membrane

. The cloacal membrane is the membrane that covers the embryonic cloaca during the development of the urinary and reproductive organs. It is formed by ectoderm and endoderm coming into contact with each other.

### 6) Urorectal septum:

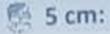
- Which is the mesodermal septum, divide cloaca into: primitive urogenital sinus anteriorly and anorectal canal posteriorly
- Separate rectum and urogenital sinus
- Maldevelopment of Urorectal septum results in recto-vaginal fistula

## Important Lengths of Various Structures

#### **应 4 cm**:

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- Cystic duct (3-4cm)
- Common hepatic duct
- Inguinal canal
- Female urethra



- Parotid duct
- Submandibular duct
- Left bronchi
- Ascending aorta
- Duodenum Ist part
- Seminal vesical (coiled)

#### 🥦 7.5 cm:

- Uterus
- Spermatic cord
- · Bile duct



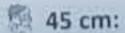
- Duodenum 3<sup>rd</sup> part
- Uterine/fallopian tube
- Abdominal aorta (10-11 cm)
- Trachea (10-11cm)
- Gall bladder (7-10cm)

#### 👰 12 cm:

- Rectum
- Pancreas (12-15cm)
- Spleen
- Pharynx (12-14cm)

#### 🥦 25 cm:

- Esophagus
- Stomach
- Duodenum
- Descending colon
- Ureter



- Spinal cord
- Vas/ductus deference
- Femur

#### Chapter 10

**GIT Physiology and Pathology** 

#### Digestion in GIT

### Carbohydrate:

- Mouth: digestion by Ptyalin of saliva: starch → maltose, maltotriose and alpha-----limit--------dextrin
- Stomach: the action of ptyalin continuous for about 1 hour, until its activity is blocked by acid
- Intestine:
  - ✓ Lactase: Lactose → glucose and galactose
  - ✓ Sucrase: Sucrose → glucose and fructose
  - ✓ Maltase: Maltose → 2 glucose

#### M Protein:

- . Mouth: NIL
- Stomach: protein-----proteoses, peptones and large polypeptide, also digest collagen
- Intestine: various enzyme split polypeptide into amino acid

#### 图 Fat:

- . Mouth: NIL
- Stomach: tributyrase digest tributyrin (a butter fat)
- Intestine: Emulsification of fat, and breakdown by various enzyme

#### Sodium and Potassium:

- In the colon, passive diffusion via Na<sup>+</sup> channels is most important. The Na<sup>+</sup> channels of the colon are similar to those in renal distal tubules and are stimulated by Aldosterone
- Potassium is either absorbed or secreted depending on the concentration in the lumen.

### Innervation of the GIT tract

#### 1) Extrinsic innervation:

- Parasympathetic NS:
  - Is usually excitatory on the function of the GI tract
  - Carried via the vagus and pelvic nerve

#### Sympathetic NS:

- Is usually inhibitory on the function of the GI tract
- Fiber originate in the spinal cord between T-8 and L-2

### 2) Intrinsic innervation: (enteric nervous system)

- Myenteric plexus (Auerbach's plexus)
  - Primarily control Motility of the GI smooth muscles
- Submucosal plexus (Meissner plexus)
  - Primarily controls Secretion and blood flow

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## PHYSIOLOGY

#### Saliva

- Tonicity: Hypotonic
- Ph---7-- freshly secreted saliva is slightly acidic
- Volume: Produce 1.5L per day or 20ml/hour
- Amylase: digestive function, hydrolysis of starch, acidic nature of saliva
- Salivary Centre---Medulla
- Inorganic constituent of saliva include: Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>+</sup>, Phosphate, iodide, Thiocyanate
- Organic constituent: contain amylase (ptyalin) and mucoprotein
- Lactoferrin-Prevent iron utilization, iron-binding protein
- Lysozyme-----Bactericidal agent
- Substance-P——A vasodilator, cause secretion in salivary gland
- Acetylcholine—increase salivary secretion
- Thiocyanate mainly occur in smoker secretions
- Alpha-1 activation produce thick saliva
- HCO<sub>3</sub> and K<sup>+</sup> in the saliva is greater than that of plasma because of their active secretion
- Under neural control not under hormonal control

Drug Secreted in saliva include	Drug Excreted by saliva and sweat: HITLER	
<ul> <li>Phenytoin,</li> <li>Theophylline and</li> <li>caffeine</li> </ul>	<ul> <li>Heavy metals,</li> <li>Potassium lodide,</li> <li>Thiocyanates,</li> <li>Lithium and</li> <li>Rifampin</li> </ul>	

#### Chapter 10

GIT Physiology and Pathology

### **GIT Hormones**



- Secreted by: mucosa of jejunum in response to fat
- Contain 33 amino acid and is homologous to gastrin

#### Stimuli for CCK:

- Small peptide and Amino acid
- Fatty acids and monoglycerides, triglyceride do not stimulate the release of CCK because they can't cross intestinal cell membranes

#### Function

- Inhibit gastric emptying and motility and Stimulate intestinal motility
- Cause contraction of gall bladder and relaxation of the sphincter of Oddi
- Act on the pancreatic acinar cell to increase enzyme secretion(lipases, amylase and proteases)
- Potentiates secretin-induced stimulation of pancreatic HCO3 secretion
- Stimulate the growth the exocrine pancreas
- CCK participate in receptive relaxation

#### Somatostatin

- Secreted by the D -cell of the islet
- Inhibits the release of growth hormones
- Inhibit the release of almost all peptide hormones
- Inhibits the release of all GI hormones
- Inhibits the release of H\* secretion
- . Inhibit gastric, pancreatic and Biliary secretion
- The GI paracrine are Somatostatin and histamine
- In pancreatic fistula, Somatostatin inhibits secretion
- VIP causes the relaxation of all GIT muscles
- Almost all factors related to ingestion of food stimulate Somatostatin secretions e.g. increase blood glucose, increase amino acid, increase FFA, infusion of IV-dextrose

- . Gastrin and CCK have the same, 5 carboxyl-terminal amino acid
- "Little gastrin" contains 17 AA and "Big gastrin" contains 34 amino-acids (AA)
- . Little gastrin is the form secreted in response to a meal

### Stimuli for the secretion of gastrin: PVD

- ✓ Small Peptides and Amino acid in the lumen of the stomach—Protein
- √ Vagal stimulation
- ✓ Distension of stomach
- √ Hypoglycemia

#### Function:

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- ✓ The main function is the stimulation of HCl and pepsin
- ✓ Increase gastric motility/contraction
- ✓ Increase ileal motility and intestinal motility
- ✓ Release of ileocecal sphincter
- ✓ Induce mass movement in the colon

#### Inhibition of gastrin secretion:

- ✓ H<sup>\*</sup> in the lumen of the stomach
- √ Somatostatin

#### Clinical Pearls:

- ✓ A secretin stimulation test is highly useful to confirm the diagnosis of Zollinger-Ellison syndrome (Gastrinoma). A rise in serum Gastrin levels greater than 200pg/ml above baseline after secretin administration is found in patient with ZES
- ✓ Gastrin level Increase by chronic use of PPI and hypoglycemia
- ✓ Phenylalanine and tryptophan are the most potent stimulant for gastrin secretion.

#### Secretin

### Stimuli for the release of secretin

- ✓ Secretin is released from the S cell of the duodenum in response to
  - o H' in the lumen of the duodenum
  - Fatty acids in the lumen of the duodenum

#### Function:

- ✓ Inhibits GIT motility
- ✓ Act on ductal cell of pancreas to secrete high quantities of HCO₃ to neutralize acid
- ✓ Inhibits H<sup>\*</sup> secretion by gastric parietal cells
- ✓ Increase HCO₃ and water secretion by the liver and increase bile production
- ✓ The 2<sup>nd</sup> messenger for secretin is cAMP

- Except in the esophagus and the proximal portion of the stomach, the smooth muscle of the gastrointestinal tract has spontaneous rhythmic fluctuations in membrane potential between about -65 and -45 mV. This basic electrical rhythm (BER) is initiated by the interstitial cells of Cajal, stellate mesenchymal pacemaker cells with smooth muscle-like features that send long multiply branched processes into the intestinal smooth muscle. In the stomach and the small intestine, these cells are located in the outer circular muscle layer near the myenteric plexus; in the colon, they are at the submucosal border of the circular muscle layer. In the stomach and small intestine, there is a descending gradient in pacemaker frequency, and as in the heart, the pacemaker with the highest frequency usually dominates.
- . The BER itself rarely causes muscle contraction, but spike potentials superimposed on the most depolarizing portions of the BER waves do increase muscle tension. The depolarizing portion of each spike is due to Ca2+ influx, and the repolarizing portion is due to K+ efflux.
- . Many polypeptides and neurotransmitters affect the BER. For example, acetylcholine increases the number of spikes and the tension of the smooth muscle, whereas epinephrine decreases the number of spikes and the tension.
- . The rate of the BER is about 4/min in the stomach. It is about 12/min in the duodenum and falls to about 8/min in the distal ileum. In the colon, the BER rate rises from about 2/min at the cecum to about 6/min at the sigmoid.
- . The function of the BER is to coordinate peristaltic and other motor activity; contractions occur only during the depolarizing part of the waves. After vagotomy or transaction of the stomach wall, for example, peristalsis in the stomach becomes irregular and chaotic.

#### Osmotic vs. Secretory Diarrhea

#### 1) Osmotic diarrhea

- Cause: excessive osmotic forces exerted by unabsorbed luminal solutes
- Effect of fasting: Relieved by fasting
- ✓ Example: lactase deficiency, lactulose and magnesium citrate

### 2) Secretory diarrhea

- ✓ Cause: increased electrolyte secretion
- ✓ Effect of fasting: Persist during fasting
- Example: toxin produced by bacterial pathogens, hormones producing tumor
- ✓ Jejunostomy plus ileostomy cause: Secretory + osmotic diarrhea

### 3) Lactose intolerance:

- ✓ Lactose intolerance is the inability to break down a type of natural sugar called lactose
- ✓ A person becomes lactose intolerant when his or her small intestine stops making enough of the enzyme lactase to digest and break down the lactose.
- ✓ When this happens, the undigested lactose moves into the large intestine.
- ✓ The bacteria that are normally present in the large intestine interact with the undigested lactose and cause symptoms such as bloating, gas, and diarrhea.
- The condition may also be called lactase deficiency.

#### Chapter 10

GIT Physiology and Pathology

#### Types of GIT Reflexes

- 1) Reflex that occurs entirely within in enteric nervous system of GIT Example:
  - ✓ Reflexes that control GIT secretion, peristalsis and mixing.
- Reflexes from GIT-----to prevertebral sympathetic ganglia (i.e. celiac, mesenteric and hypogastric ganglia)------back to GIT Example:

#### √ Gastrocolic reflex:

- Signals from stomach cause evacuation of the colon, stomach activity leads to ileocecal relaxation and increased mass movement of the colon
- Gastro colic reflex moves feces into the rectum
- The response is strongest after breakfast
- New born children routinely defecate after meal

#### ✓ Enterogastric reflex:

- When fat or protein chyme reaches the duodenum, receptors detect and send the impulse to the enteric nerve of the stomach that in turn cause the inhibition of stomach motility and secretion
- o Delays emptying
- ✓ Colonoileal reflex: Signals from colon inhibit emptying of ileal contents
- 2) Reflexes from GIT------back to GIT Example:
  - · Pain reflex
  - Defecation reflexes:
    - O Defecation is the combination of intrinsic defecation reflex and parasympathetic defecation reflex

### 3) Migrating motility complex (MMC):

- 1. MMC starts at the stomach each about 90min to reach the large intestine
- 2. MMC is called the intestinal housekeeper
- 3. MMC is regulated by hormone Motilin at a rate of 5cm/min
- 4. Motilin hormone is secreted by the endocrine cell of small intestine mucosa
- 5. Intestinal motility: there are three types of contraction: peristaltic contraction, segmentation contraction, and tonic contraction, the slow wave in the small intestine muscle are tonic contraction
- 4) Peristalsis: during and following meals --- movement of 2-25cm/sec
  - Waves that move a bolus along the length of the digestive tract

GIT Physiology and Pathology

- The circular muscle behind the bolus contract and the one ahead relaxes
- Longitudinal muscles ahead contract next and shorten adjacent segment
- Primary peristalsis:
  - ✓ Esophageal peristaltic contraction wave associated with swallowing
  - Cannot occur after Vagotomy
- Secondary peristalsis:
  - ✓ Involuntary wave, not associated with swallowing and does not involve full swallowing reflex
  - Can occur after Vagotomy
  - Caused by local distention in an attempt to clear the esophagus
  - ✓ Initiated in the smooth muscle of the lower esophagus



#### Defecation



#### Defecation:

- The Process by which feces are expelled through the anus is called defecation
- The Desire for defecation:
  - Is normally initiated when a mass movement force feces into the rectum

#### Defecations reflexes:

- > Weak intrinsic defecation reflex: Feces enter rectum -> distention of rectal wall -> afferent signals spread through myenteric plexus ->peristaltic wave initiates in descending colon, sigmoid colon and rectum, forcing feces toward anus -> internal anal sphincter is inhibited (relaxed) → if external anal sphincter is also relaxed by will → defecation occurs
- > Parasympathetic defecation reflex: Feces in rectum -> afferent fibers in rectum stimulated -> afferent signals passes to the sacral segment of spinal cord -> efferent signals passes through the pelvic nerve to descending colon, sigmoid colon, rectum and anus → causes following effects
  - ✓ Relax internal anal sphincter
  - ✓ Convert weak intrinsic defecation reflex into powerful peristaltic waves
  - ✓ Cause deep breath, closure of glottis, contraction of abdominal muscle and descending of the pelvic floor -> all these effects promote emptying of the rectum → if external anal sphincter is also relaxed by will → defecation occurs

### Stimuli for the mass movement

- ✓ Gastrocolic and duodeno-colic reflexes afterthe meal
- ✓ Initiation in the colon (e.g. ulcerative colitis)
- ✓ Intense parasympathetic stimulation
- ✓ Overdistension of a segment of colon

## **PATHOLOGY**

Gastric Ulcer	Duodenal Ulcer
Less common	Most common
<ul> <li>70% of gastric ulcer patients are infected with H.pylori and the remaining 30% of gastric ulcer is caused by NSAIDs.</li> </ul>	Around 90% of duodenal ulcer patients are infected with H.pylori.
Gastric ulcers most commonly occur in lesser curvature within the antrum.	The Chronic <u>duodenal ulcer</u> usually occurs in the <u>first part of the</u> <u>duodenum</u> and 50% on the anterior wall
Risk of malignancy is <u>more in gastric</u>	<ul> <li>Duodenal ulcer almost neve malignant</li> </ul>
<ul> <li>In <u>Gastric</u> ulcer, Pain is <u>Greater</u> with eating (weight loss)</li> </ul>	In <u>Duodenal</u> ulcer, pain is more common in the night and <u>Decrease</u> with eating (weight gain).
Gastric ulcer erodes left gastric artery	<ul> <li>Duodenal ulcer erodes gastroduodena artery</li> </ul>

#### **Chronic Gastritis**

Type A Chronic Gastritis	Type B Chronic Gastritis
the body and fundus and spares the antrum	<ul> <li>it is the <u>most common type</u> of chronic gastritis and are due to <u>H.pylori</u> <u>infection</u></li> </ul>
There is 4 fold increased risk of gastric     Adenocarcinoma.	<ul> <li>It involves the antrum and pylorus.</li> <li>There is an increased risk of MALT lymphoma.</li> </ul>
It is due to Autoantibodies against intrinsic factor causing pernicious anemia.	The predominant inflammatory cells are Lymphocytes and plasma cells.

Premalignant Lesions	Premalignant Condition	
Leukoplakia	Oral submucous fibrosis (complication o pan chewing)	
Erythroplakia Carcinoma in situ Leukokeratosis nicotina palatinae	Actinic keratosis	
	Syphilis	
	Oral lichen planus	
	Discoid lupus erythematosus	
	Sideropenic dysphagia	

## Oral cavity

- Hematemesis: Vomiting of blood: Duodenal ulcer> Gastric ulcer> Esophageal ulcer
- Hematochezia: Loss of bright red blood per rectum: Diverticulosis is the most common cause followed by Angiodysplasia.
- Fecal Occult blood: Blood in the stool that can't be seen with the naked eye.
- Melena: It refers to black tarry stools from digested blood = it is mostly due to upper GI bleeding like peptic ulcer disease etc.
- Esophageal atresia: at birth esophageal atresia should be suspected where there is salivation and frothing out of mouth and nose
- Cleft lip/palate, most common congenital disorder of oral cavity
- Erythroplakia is associated with much greater risk of malignant transformation than Leukoplakia. Simply: Leukoplakia (most common) and Erythroplakia (most lethal)

#### Salivary Gland

- There are three major pairs of salivary glands: Parotid gland, Submandibular gland, Sublingual gland and many other salivary glands throughout the oral cavity.
- The Parotid gland is the most common site for salivary gland tumors, the most common tumor of the salivary gland is pleomorphic adenoma (mixed tumor) and parotid gland is the most common site for pleomorphic adenoma, present as painless, moveable mass at the angle of jaw.
- Mucoepidermoid carcinoma is the most common malignant tumor of the salivary gland in the adult and has mucinous and squamous components. It can present as a painless mass (low grade) initially or painful mass (high grade) because of the common involvement of the facial nerve.
- Development of salivary gland: they originate from oral epithelial buds invading the underlying ectomesenchyme. The origin of epithelial buds ectoderm in parotid and minor salivary gland, Endodermal in submandibular and sublingual glands

#### Naseem Sherzad High-Yield Points

- . The most common site of oral cancer in the world : tongue
- . Most common histological variety of oral cancer is: Squamous cell carcinoma
- Most common histological variety of lip carcinoma is: Squamous cell carcinoma
- · Oral malignancy with the best prognosis: Lip cancer
- The most common site of Ca lip: Lower Lip
- · Oral malignancy with worst prognosis: Floor of mouth
- The most common site of carcinoma tongue is middle of lateral border

#### Chapter 10

#### GIT Physiology and Pathology

#### Esophagus

- 1) Most common congenital anomaly of the esophagus is tracheoesophageal fistula
- 2) Odynophagia which means painful swallowing; esophagitis is the most common cause of Odynophagia. GERD is the most common cause of esophagitis

#### **Mallory Weiss syndrome**

#### Weiss Mallory longitudinal/linear/vertical tear (non-Transmural) below the gastroesophageal junction that is induced by repetitive and strenuous vomiting.

- Present with painless hematemesis
- Not a full perforation
- Most of the time (90%) the bleeding from Mallory Weiss syndrome will stop without any intervention

#### **Boerhaave Syndrome**

- Transmural esophageal rupture due to violent retching
- Although Boerhaave syndrome classically presents as the Mackler triad of chest pain, vomiting, and subcutaneous emphysema due to esophageal rupture, these symptoms are not always present.
- The most common anatomic location of the tear in Boerhaave syndrome is at the left posterolateral wall of the lower third of the esophagus, 2-3 cm proximal to gastroesophageal junction, along longitudinal wall of the esophagus.

#### Achalasia

- A-chalasia is due to the Absence of myenteric plexus and there is Absence of relaxation.
- Decrease level in the expression of NO synthase
- Achalasia is associated with an increased risk of esophageal Squamous cell carcinoma.
- Barium swallow shows Bird's beak/Rattail/Root appearance in Achalasia.
- Esophageal manometry is the gold standard test for Achalasia.
- In Achalasia, dysphagia occurs for both solid and liquid at the same time.
- In esophageal carcinoma, there is progressive dysphagia (initially for solid than for both solid and liquid)

#### Barrett's Esophagus

- Barrett's esophagus refers to an abnormal change (metaplasia) in the cells of the lower portion of the esophagus. It is characterized by the replacement of the normal stratified squamous epithelium lining of the esophagus by simple columnar epithelium
- \* Complication: the most common complication is ulceration with stricture formation and the second common is Adenocarcinoma.
- Endoscopic biopsy is the investigation of choice for Barrett's esophagus.
- Adenocarcinoma in the people with long-standing GERD occurs in the distal one third----1/3. Barrette esophagus is the most common predisposing factors
- Squamous cell carcinoma is most common esophageal cancer worldwide, which occurs most commonly in the upper two-third-2/3 of the esophagus (upper 3<sup>rd</sup>-15%, middle third-50%). Smoking (most common cause), betel chewing & alcohol are the main risk factors.

### **Esophageal Tumors**

#### i. Benign tumor:

- The most common benign tumor of the esophagus is Leiomyomas
- · Other tumors:
  - √ Fibroma
  - √ Lipomas
- ii. Esophageal carcinoma: 6th most common cancer in the world:

#### Types:

- Squamous cell carcinoma: commonest, upper two-third of the esophagus, associated with smoking >alcohol
- Adenocarcinoma: Lower one-third of the esophagus and most common in western world

### Stomach and Duodenum

- 1) The most common cause of upper GI bleeding is peptic ulcer disease (60%) and the most common site from the peptic ulcer is the posterior part of duodenum.
- The most common cause of lower GI bleeding is Diverticular disease.
- 3) Curling ulcer-Burn: Mnemonic-"Burned by the curling iron"-decrease plasma volume lead to sloughing of gastric mucosa
- Cushing ulcer-Brain injury: Mnemonic "Always Cushion the brain" -- increase vagal stimulation which increases ACh and causes increase production of H
- Neutrophil are the predominant inflammatory cell in acute gastritis.
- Stomach is the most common site for extra-nodal non-Hodgkin's lymphoma.
- Gastric lymphoma (MALToma) is the only malignancy that can be treated with antibiotics.
- Microbiological culture is the gold standard diagnostic test for H-pylori infection
- The most common malignant tumor of the small intestine is adenocarcinomas. The Most common site for adenocarcinomas of the small intestine is the duodenum

#### **Pyloric Stenosis**

- NAME AND ADDRESS OF THE OWNER, WHEN PERSON NAMED IN Classically presents two weeks after birth with projectile nonbilious vomiting, visible peristalsis (you can see), olive-like mass in abdomen (you can feel) and give splash sound on auscultation (you can hear).
- · Hypochloremic, hypokalemic metabolic alkalosis with paradoxical aciduria is the classic electrolyte and acid-base imbalance of pyloric stenosis.

#### Duodenal atresia

- . It is typically characterized by the onset of vomiting within hours of birth (regurgitation of the first feed)
- X-ray supine abdomen show "double bubbles sign"

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Duodenal atresia-----Bilious vomiting, pyloric stenosis: non Bilious vomiting

### Peptic Ulcer Disease (PUD)

- It is characterized by the formation of ulcer that occurs in any portion of GIT.
- The most common cause of death in peptic ulcer is perforation. The content of the stomach enter into the peritoneum and cause peritonitis and shock and can even lead to death. The most

#### Chapter 10

GIT Physiology and Pathology

frequent site for perforation is the anterior wall of the first part of the duodenum.----(Anterior(AP)----Perforate and Posterior(BP)------Bleed)

- The most common complication of peptic ulcer is hemorrhage.
- Perforation, bleeding and gastric outlet obstruction are the most common complication of peptic ulcer disease.

#### **Gastric Carcinoma**

- Stomach carcinoma is almost always Adenocarcinoma
- Blood group A has an increased risk of gastric carcinoma (intestinal type) and blood group O has increased risk of duodenal ulcer.
- Lauren classification of gastric carcinoma: histological subtype
  - Intestinal type: This is the most common; arise from intestinal metaplasia and having expanding growth pattern.
  - Diffuse type: it arises from normal gastric mucosa and having infiltrating growth pattern. Desmoplasia results in the thickening of the stomach wall (linitis plastic). Signet ring cell carcinoma (the nucleus is pushed to one side and look like the ring) is defined when greater than 50% of the tumor is formed by signet cells, which occur in diffuse type of gastric carcinoma.

#### Metastasis of gastric carcinoma

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- Troisier's sign: Spread occurs to the left supraclavicular lymph nodes (Virchow node)
- Sister Mary Joseph's nodules: To periumbilical region, seen with intestinal-type
- Krukenberg tumor: Bilateral ovaries—seen with diffuse type

### The Small and Large Intestine



- 1) Rotavirus is the most common cause of childhood diarrhea.
- 2) The hallmark of malabsorption is steatorrhea (fats in stool) and chronic diarrhea.
- 3) Malabsorption syndrome: can causes diarrhea, steatorrhea, weight loss, weakness, vitamin and mineral deficiency. Screen for fecal fat e.g. Sudan stain.
- 4) Please remember that Vitamin B12 absorption occurs in Terminal Ileum so any disease which effect terminal ileum will be having Vitamin B12 deficiency like crohn's disease and ileal resection
- 5) Sigmoid colon: Most common site for colorectal carcinoma, volvulus and Diverticulosis
- 6) Red currant jelly stool is a characteristic finding in Intussusceptions. Remember that currant jelly sputum is characteristic finding in Klebsiella.
- 7) Diverticulitis is sometimes called "left-sided appendicitis" due to overlapping clinical presentation. However, appendicitis is on the right side and diverticulitis is on left side.
- 8) The Rectum is always and always involved in ulcerative colitis and in the Crohn's disease terminal ileum is the most common site.
- 9) Smoking and appendectomy have a protective effect on ulcerative colitis.
- 10) Meconium Ileus: Most common cause is cystic fibrosis and most common site is terminal ileum

## Intestinal Polyposis

- Polyps are the most common benign tumor of the stomach.
- The Sigmoid colon is the most common site for polyps
- · Polyp may be of the following types:
  - Hyperplastic polyps
    - Most common colonic polyp type,
    - ✓ Benign, no malignant potential
  - Adenomatous polyps:
    - √ Villous adenoma:
      - Worst type
      - Sessile type with predominantly villous appearance
      - O Villous adenoma of colon can result in watery diarrhea and hypokalemia
    - ✓ Tubular adenoma is the most common type and looks like a strawberry on a stick
    - ✓ The risk for cancer greatest when polyp> 2cm and has increased villous component.

### Familial Adenomatous Polyposis

- . Inheritance= Autosomal dominant, a mutation on Adenomatous polyposis coli (APC) gene on chromosome 5
- . Classic AFP: >100 colonic adenomas required for diagnosis, 100% risk of progression into colon cancer.

#### Hamartomatous Polyp

- These are malformation of the gland and mucosa.
- Classification:
  - Juvenile polyp 1-3 cm in diameter (no malignant potential)
  - Retention polyp (no malignant potential) Peutz-jeghers syndrome: Autosomal dominant
  - Juvenile polyposis syndrome (50-100 juvenile polyp)

### Naseem Sherzad High-Yield Points

- Gardner Syndrome = FAP plus osteoma, epidermal cyst and fibromatosis
- Turcot Syndrome = FAP plus malignant CNS tumor-----Turcot-Turban
- · Gardner syndrome and turcot syndrome is the two extra-intestinal feature of familial Adenomatous polyposis.
- Polyp: Polyp is a mucosal growth that protrudes into the lumen of the gut. It could be sessile or pedunculated and 90% are non-Neoplastic
- Polyposis means multiple polyp
- Polyposis syndrome is hereditary, characterized by the presence of multiple sessile or pedunculated tumors of the mucosa.

### Chapter 10 Hirschsprung's Disease

- Also known as "Congenital Aganglionic Megacolon", it is associated with Down syndrome.
- It is due to the lack of both Meissner submucosal and Auerbach's myenteric plexuses in the distal portion of intestine.
- Rectal biopsy: This test gives the definitive diagnosis. Full thickness rectal biopsy 2-cm above the dentate line done in old children will reveal the lack of ganglion cells. In neonate suction rectal biopsy can be performed at the bedside

#### Meckel's Diverticulum

- Definition: It is a congenital diverticulum arising from the antimesenteric border of the ileum
- The Persistence of the proximal portion of the vitelline duct is called Meckel's diverticulum.
- Most common congenital anomaly of GIT is Meckles diverticulum
- Contains all three layer of bowel with independent blood supply
- If the Meckel's diverticulum is found in an inguinal or femoral sac----litter's hernia
- Diagnosis: A technetium 99m pertechnetate scan, also called meckel scan
- Rule of 2'S:

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- ✓ Present in 2% of the population
- ✓ 2 feet proximal to the ileocecal valve
- ✓ Measures 2 inch in length
- ✓ Heterotrophic tissue: 2 types of common ectopic tissue
  - Gastric mucosa
  - Pancreatic acini

#### **Carcinoid Tumor**

Reference: Bailey & Love's Short Practice of Surgery, 27th Edition, Page 1315

- Most commonly occur in the appendix. The next common site is the ileum.
- The tumor can occur in any part of the appendix, but it is frequently found in the distal third
- · Carcinoid syndrome is Paraneoplastic syndrome comprising signs and symptoms that occur secondary to Carcinoid tumors and occur only if metastasis to the liver.
- Positive for chromogranin and "Dense core bodies" seen on Electron Microscope
- It can produce a number of vasoactive peptides, most commonly serotonin

### Colorectal Carcinoma or Colon Adenocarcinoma

- Left-sided bowel diameter is less than right-sided, therefore tumor tend to obstruct, fresh bright red blood coat the stool because no time to mix the blood. Left-sided carcinoma grows as a "napkin-ring" lesion. (left-Obstruct)
- Right-sided diameter is greater than left-sided therefore tumor tends to bleed and carcinoma grows as raised lesion (Polypoidal), cause Melena (bloody stool) iron deficiency anemia, mass in RIF and blood mixed with stool. (Right-Bleed)
- Rectosigmoid colon (descending colon) is the most common site.

- Colonoscopy with biopsy is the gold standard test for colon Adenocarcinoma.
- Occult blood testing, can help in the diagnose of colonic carcinoma.
- Strong correlation with colorectal carcinoma is seen in familial Adenomatous polyposis (FAP).
- Villous adenoma has the greatest risk of developing colon cancer.
- There is an increased risk for streptococcus Bovis Endocarditis in these patients.
- Metastasis to regional lymph node is most common and distant metastasis is most common to
- A CEA level is most useful as a marker for postoperative recurrence in colorectal cancer. A level is obtained every 3 months during the first 2 years after surgery to detect early recurrence that is amenable to treatment. Use of CEA as a screening test for colorectal cancer is not recommended Although preoperative elevation of CEA is an indicator of poor prognosis

Celiac Disease

- Celiac sprue is also known as "Gluten sensitive enteropathy"
- ❖ Damage is most prominent in duodenum, jejunum and ileum are less involved
- Celiac sprue is also associated with <u>dermatitis herpetiformis</u> and type I DM.

Pathogenesis:

- " It is characterized by T-cell and IgA mediated response against gluten in a genetically susceptible individual, resulting in loss of small bowel villi and malabsorption
- It is associated with HLA-DQ2 and HLA-DQ8
- Highest incidence in infancy

#### Lab Findings:

" Antibodies:

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- ✓ Anti-Gliadin antibodies: IgG and IgA anti-Gliadin are present in more than 90 % of cases.
- ✓ IgA endomysial antibody: It has sensitivity and specificity in more than 90% of cases
- ✓ Tissue transglutaminase antibodies: Have sensitivity and specificity more than 95 %

\* Biopsy:

- ✓ Endoscopic mucosal biopsy of distal duodenum or proximal jejunum is the Gold standard method for confirmation of diagnose in patient with positive serological (antibody) test for celiac disease
- Small bowel follow-through: it shows dilation of small bowel

Morphology:

- \* Increased number of intraepithelial CD8+ T-cells, with intraepithelial lymphocytosis, Cryp hyperplasia and villous atrophy.
- \* Increased epithelial regeneration, increased crypt mitotic activity and increased immature enterocytes
- Increased number of plasma cells, mast cells and eosinophils especially within the upper part of lamina propria
- Increase in number of intraepithelial lymphocytes, particularly within the villus, is a marker the mild form of celiac disease

### Liver, Gallbladder and Bile Ducts

- Mallory -Denk bodies are the morphological feature of alcoholic fatty liver disease
- Mallory body: Which is intermediate filament cytoplasmic inclusion and is seen in Alcoholic hepatitis
- 3) Hobnall liver: Alcoholic cirrhosis

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- 4) Councilman body: Councilman Body formed during the process of apoptosis which represents dead hepatocyte which is seen in viral hepatitis and Toxic hepatitis.
- 5) Fibrotic changes are characteristic in chronic hepatitis
- 6) Acetaminophen is the leading cause of drug-induced acute liver failure
- 7) Polycythemia Vera is the most common cause of hepatic vein thrombosis
- 8) The most common cause of Pyogenic liver abscess is ascending cholangitis. Most common in immunocompromised and in people with liver cirrhosis
- 9) Fatty liver is most often caused by increased synthesis of TGs and less commonly by problem related with the packing of TGs into VLDL or its secretion into blood
- 10) Carcinoma of the gallbladder is the most common malignancy of the extrahepatic Biliary tract
- 11) Unconjugated hyperbilirubinemia is increased in all Hemolytic anemia, which can also lead to black stone formation, a type of pigment stone.
- 12) Bronze diabetes means Hemochromatosis of the liver plus pancreas and skin.
- 13) Hemosiderin or haemosiderin in an iron storage complex. It is an insoluble protein that contains iron produced by a phagocytic lesion of hematin that is released during hemolysis of hemoglobin and found as a granule in most tissue, especially liver.
- 14) Hemosiderosis it is a focal deposition of iron that does not cause tissue damage. In hemosiderosis usually, the lungs are affected, and the cause usually is recurrent pulmonary hemorrhage, either idiopathic or due to chronic pulmonary hypertension. Another common site of accumulation is the kidneys, where hemosiderosis can result from extensive intravascular hemolysis.
- 15) There is an association of between Choledochal cyst and Hepatobiliary cancer, most commonly Cholangiocarcinoma
- 16) Hemochromatosis (iron overload) is a typically systemic process in which iron deposition can cause tissue damage (this damage is mediated by the generation of free radical). It may be primary (due to mutation in HFE gene, most commonly C282Y) or secondary (due to complication of blood transfusion). In Hemochromatosis, daily mucosal absorption of iron is 4mg or more
- 17) Fatty liver:
  - ✓ Malnutrition is one of the major cause of fatty liver
  - ✓ Malnutrition is the major cause of fatty liver in Pakistan and underdeveloped countries
  - ✓ Alcohol is the most important cause of fatty liver in the world or in advanced countries

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Wilson's disease

- Low serum ceruloplasmin-----Single best laboratory clue to diagnose
- Kayser-Fleischer ring in the eye ---- Single best clinical clue to the diagnose
- The gold standard for diagnosis remains liver biopsy with quantitative copper assay

#### Liver Cirrhosis

- Nutmeg liver develops due to Passive congestion of the liver.
- Liver cirrhosis is the most common cause of portal hypertension.
- Hepatitis B and C are the most common cause of liver cirrhosis worldwide while the alcoholic liver disease is the most common cause of liver cirrhosis in the West.
- Liver cirrhosis when look grossly may be either Micro-nodular= <3mm or Macro nodular = >3mm or Mixed micro and macro-nodular.
- Serum albumin and prothrombin time (PT) are the best indicators of liver function. The Explanation given below:
- The half-life of albumin in circulation is long (about 20 days), and the half-life of blood clotting factors is quite short (about 1 day). Thus, albumin levels decrease when cirrhosis occurs, and they have prognostic meaning in these patients. On the contrary, patients with acute, massive hepatocellular necrosis (acute toxic or viral hepatitis) may have a brisk increase in prothrombin time (usually <3 seconds) that tends to plateau, and normal albuminemia. In these patients, prothrombin time can be monitored in order to assess the risk of acute liver failure. In nutshell: CLD------PT will be low------------PT will be deranged

#### Primary Sclerosing Cholangitis (PSC)

- . It is characterized by progressive inflammation, fibrosis and stricture of extra-hepatic and intrahepatic bile ducts.
- Beading appearance (multiple areas of bile duct stricture and dilations) show on cholangiography performed endoscopically or with aid of MRI is specific feature of primary sclerosing cholangitis.
- It increases the risk of Cholangiocarcinoma.
- It shows "onion skin" appearance due to fibrosis and inflammation of peri-ductal portal tract and when lumen disappears just leaving a dense button of scar, which is called "Tombstone scar".
- It is associated with ulcerative colitis (most common), retroperitoneal fibrosis, chronic hepatitis and HIV infection

#### Primary Biliary Cirrhosis (PBC)

- It is characterized by the destruction of the intrahepatic bile duct.
- Primary Billary cirrhosis is associated with celiac disease, Raynaud's disease, Sjogren syndrome and systemic sclerosis
- Diagnose is made by Anti-mitochondrial antibody (AMA) and typical biopsy --- biopsy is the best test to diagnose.
- Itching, pruritus before jaundice and middle-aged women are the clues that help in diagnosis.

#### **Liver Tumors**

#### Hemangioma:

- ✓ It is the most common benign tumor of the liver.
- ✓ It is not a pre-cancerous condition and not associated with oral contraceptive
- · Chronic hepatitis B and C, cirrhosis and aflatoxin are the major causes of hepatocellular carcinoma or hepatoma.
- The most common, overall, the hepatic tumor is metastatic/secondaries and colorectal carcinoma is the most common primary site.
- Cavernous hemangioma is the most common primary benign tumor of the liver
- Hepatocellular carcinoma is the most common primary malignant tumor of the liver and Cholangiocarcinoma, the second most common hepatic malignant tumor after HCC.
- Screening for hepatocellular carcinoma by ultrasound and AFP at a 6-months interval is indicated in the high-risk patient.
- Alpha-fetoprotein is the tumor marker of hepatocellular carcinoma.

- 1) Pseudo-cyst, hemorrhage, abscesses and ARD are the most common complication of acute pancreatitis. 75 % of the cyst in the pancreas is pseudo-cyst.
- 2) Serum lipase is the most specific test for diagnosis of acute pancreatitis.
- 3) The most common cause of chronic pancreatitis is long-term alcohol use.
- 4) Hemorrhagic pancreatitis is the most severe form of acute pancreatitis, which may be secondary to Elastase, which causes break down of elastin inside the blood vessels and leak red blood cell to the pancreas.
- 5) Malabsorption and diabetes mellitus are the two common complication of chronic pancreatitis.
- 6) Among islets cell tumor the most common tumor is insulinoma which produces insulin and causes hypoglycemia. Insulinoma can be diagnosis by an increased level of c-peptide.
- 7) Gastrinoma is often malignant tumor and it produces gastrin.
- 8) The commonest site for pancreatic neoplasm is the head of the pancreas. (Head 60%, body 15%, tail 5% and entire gland 20%)
- 9) Carcinoma of the head of the pancreas present with obstructive jaundice, pale stools and palpable gall bladder. Carcinoma of tall or body presents with secondary DM.
- 10) K-RAS is the most commonly affected oncogene in carcinoma pancreas in the early stage and p-16 is the most commonly affected tumor suppressor gene in the intermediate stage
- 11) Most common benign tumor of the pancreas is the cyst adenoma

#### Chapter 10

### Jaundice

	ON THE PERSON NAMED IN	Features
Jaundice after birth	. Jaundice on the 2"	dayPathological
Hemolytic jaundice	■ It is caused by:  ✓ Hereditary  ✓ Sickle cell a  ✓ Hemolytic  ✓ Warm aut	disease of newborn oimmune hemolytic anemia
Gilbert's syndrome	<ul> <li>Autosomal dominant</li> <li>Gilbert's syndrome produces an elevated level of unconjugated Bilirubin in the bloodstream, but normally has no serious consequences.</li> <li>Mild jaundice may appear under conditions of exertion, stress, fasting, and infections, but the condition is otherwise usually asymptomatic.</li> </ul>	
Rotor syndrome	<ul> <li>Autosomal recessive</li> <li>Asymptomatic, benign defective uptake an storage of conjugated Bilirubin, possibly in the transfer of Bilirubin from the liver to bile</li> </ul>	
Dubin-Johnson syndrome	<ul> <li>The rare autosomal recessive inherited disorder</li> <li>Removal of conjugated Bilirubin from the liver ce and the excretion into the bile are defective</li> <li>Classically, the condition causes a grossly black liver due to the deposition of a pigment similar melanin.</li> </ul>	
	Crigler-Najjar d	isease
Type-I		Type-II
Autosomal recessive     Absent Bilirubin glucuro	nyltransferase	Autosomal dominant     Deficient glucuronyltransferase     Kernicterus is Nove

#### **Acute Pancreatitis**

- Definition: It refers to acute inflammation of the pancreas.
- \* Pathogenesis: It is due to the autodigestion of pancreatic parenchyma by the pancreatic enzyme. The first enzyme that activates prematurely is trypsin, which leads to the activation of enzyme.

#### Causes: Mnemonic "GET SMASHED"

- Gallstone--most common cause
- Ethanol-alcohol
- Trauma

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- Steroids
- Mumps
- Autoimmune
- Scorpion venom
- Hyperlipidemia and Hypercalcemia
- Endoscopy (ERCP)
- Drug like thiazide diuretic and azathioprine

#### Investigation for acute pancreatitis:

-

- Elevated serum amylase in the first 24 hours(> 1000U/ml), should rise thrice of normal
- Serum lipase: This is the most sensitive and specific method, should
- Contrast-enhanced CT-scan: This is the best imaging study
- Abdominal X-ray: show sentinel loop sign and colon cut off sign

#### Important sign

- Cullen sign: irregular hemorrhagic patches around the umbilicus
- Grey turner sign: refers to bruising of the flanks

#### **Biliary Atresia**

- Failure of the bile ducts to canalize during development causes atresia.
- Jaundice appears soon after birth, clay-colored stools and very dark colored urine are also present.
- Surgical correction of the atresia should be attempted when possible.
- If the atresia cannot be corrected, the child will die of liver failure.

#### Viral Marker of Hepatitis B

Hepatitis B virus protein act as an antigen to which infected person can make antibody. These antigens and their antibody are important in identifying hepatitis B viral infection; these are called viral markers.

#### I. Hepatitis B surface antigen( HBsAg):

- \* This is the first marker and the first detectable viral antigen to appear during infection
- It became undetectable usually after 1-2 months after the onset of jaundice and rarely persists beyond 6 months. If it present beyond 6 months that define the chronic state

### ii. Antibody to hepatitis B surface antigen (anti-HBs):

- Anti-HBs appear usually after clearance of surface antigen.
- The Presence of these antibodies (IgG) indicates previous infection (resolved) or vaccination.

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Kernicterus is NOT common

Fatal in infancy secondary to kernicterus

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### GIT Physiology and Pathology

- Disappearance of HBsAg and appearance of anti-HBs indicated recovery from HBV infection.
- It is a protective antibody.
- Occasionally appearance of anti-HBs is delayed for several weeks after the disappearance of Surface antigen (no antigen and no anti-body detectable); this is called the window period.
- During window period anti-HBc (c=core)-IgM is the only serum marker for HBV infection.

### iii. Hepatitis B core antibody (anti-HBc):

- Seen in window phase
- Acute infection= anti-HBc IgM class, and in chronic infection= anti-HBc IgG class
- It is the first antibody to appear. It appears shortly after HBsAg is detected.

### iv. Hepatitis B e antigen (HBeAg):

It indicates active viral replication and infectivity.

#### v. Hepatitis B virus DNA:

 The presence of hepatitis B virus DNA in serum is the most sensitive marker of viral replication and infectivity. It can be detected by PCR

Summary: HBs- antigen=first antigen appear and first marker-window period start -----during this phase hepatitis B core antibody appear which is the first antibody to appear---- and last is anti-HBs antibody appear.

Recovery from hepatitis B infection occurs within 6 months and is characterized by the appearance of the anti-body to viral antigen. The Persistence of HBeAg beyond this time indicates chronic infection. HBeAg is present in parallel to HBV-DNA in Blood.

#### **Liver Function Test**

## i. LFTS Part 1: Transaminase: (Vit B-6 act as a coenzyme for this enzyme)

Both of the enzymes are present in hepatocyte because these enzymes are present in hepatocyte we also called them hepatocellular enzymes because they are the marker of hepatocellular injury.

### a) Alanine Transaminase: (ALT)

- It is present in cytosol, it is specific for liver cell necrosis
- Viral or drug-induced hepatitis: ALT>>AST
- Raised in trauma to the liver

### b) Aspartate Transaminase (AST)

- It is present in mitochondria
- Alcoholic hepatitis =AST>>ALT (because alcohol is a mitochondrial toxin)

# ii. LFT Part 2: Cholestatic Jaundice or Obstructive Jaundice:

These enzymes are elevated in extra-hepatic and intra-hepatic obstruction.

- Conjugated hyperbilirubinemia
- Elevated alkaline phosphates (ALP)
- Elevated gamma glutamyl transferase (GGT)

### a) Alkaline Phosphates (ALP)

It is present in duct epithelium and Canalicular membrane of the hepatocyte

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GIT Physiology and Pathology

- Its elevation is characteristic of Cholestatic jaundice
- b) Gamma-glutamyl transferase:
  - It is elevated in extra and intrahepatic obstruction to bile flow.
  - Increased ALT and GGT= Cholestatic jaundice
- Clinical Notes: Alkaline phosphates is also produced by the bone, GIT and Placenta so ALP maybe increasing in these condition, one simple way to know that source is liver or not. Following is the simple way to differentiate:
  - Increase ALP but normal GGT = source other than liver
  - Increase ALP and GGT = Cholestatic jaundice.
  - Pregnant-lady with bile duct obstruction diagnostic investigation is: GGT
  - . Bile duct obstruction in Non-pregnant lady or male: ALP
  - The Test used to differentiate between the type of jaundice: GGT

### Difference between Ulcerative Colitis and Crohn' Disease

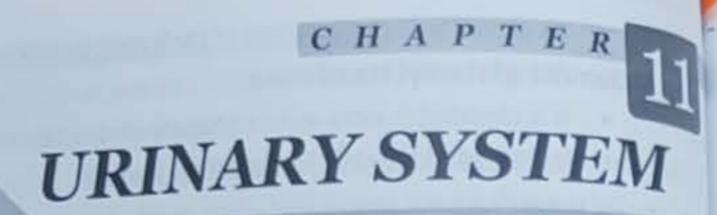
#### Two Word vs. one Word

Ulcerative colitis (2 words) (Left-sided cramping pain)	Crohn's (one word) (Right lower quadrant colicky pain)
Pseudo polyps	Fistula
Ankylosing spondylitis	Stone
Sclerosing cholangitis	Lymphocyte
Mucosa and submucosa	Transmural
Crypt abscess	Granuloma
Pyoderma gangrenosum	Obstruction
Adeno carcinoma	Stricture
Backwash ileitis	"String" sign
Lead pipe, Toxic megacolon	Skip lesion & Apthous ulcer( exception)
No smoking, P-ANCA (positive)	Smoking (strong association) important ASCA (Positive)

### Three Whipples

- \* Whipple's disease: infection with tropheryma whipplei (gram-positive), PAS-positive macrophages in the intestinal lamina propria, mesenteric lymph nodes.
- \* Whipple's triad: it is a collection of three criteria that suggest a patient's symptoms result from hypoglycemia that may indicate insulinoma: Hypoglycemia symptoms, low blood sugar <50mg/dl and symptoms relief with glucose intake
- \* Whipple procedure: also known as pancreaticoduodenectomy involve removal of the head of the pancreas, duodenum, the portion of the common bile duct and sometimes part of the stomach

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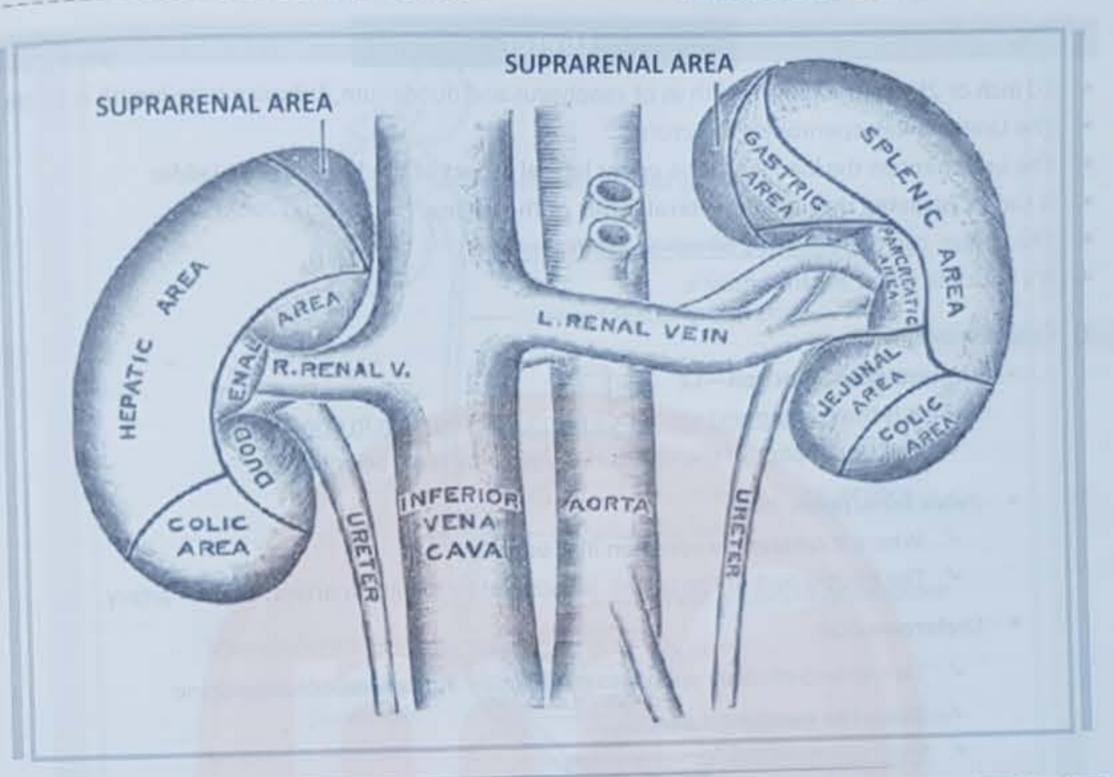


#### Kidney

- They extend from lumbar vertebra T12 to L3
- . Epithelium of kidney and trigone of bladder is derived from------Mesoderm
- · Renal column present in the cortex and contain-Inter-lobar artery
- -Collecting ducts
- -Cortex \* Renal corpuscle are located in-
- . The medulla is made primarily of-----Collecting ducts
- In intravenous urogram (IVU) of kidney, the most prominent structure is——Calyces
- . Each kidney is completely surrounded by perirenal fat which extends in the renal pelvis, Around the perirenal fat, is a layer of renal fascia called the Gerota's fascia
- . The Capsule of kidney prevent infection from one kidney to other kidney because kidney and retroperitoneal organs
- . The renal fascia or Gerota's fascia is a layer of connective tissue encapsulating the kidneys and the adrenal glands. The renal fascia separates the adipose capsule of the kidney from the overlying pararenal fat.
- . The renal fascia must be incised in any surgical approach to this organ
- . Correct Sequences of blood flow: Renal artery ---- inter-lobar arteries --- Arcuate arteries -inter-lobular arteries-afferent arterioles (Primary arterioles that provide incoming blood to the glomerulus.)----glomerulus capillary----efferent arterioles-----peritubular capillaries/vasa recta
- \* Renal angle: The angle lies between the last rib (12th rib) and lateral border of sacrospinalis is called renal angle
- . Hilum of kidney: Hilum extend into Large Cavity called the Renal Sinus
  - Structure from anterior to posterior—VAUA
    - ✓ Renal Vein
    - ✓ Renal Artery 2 branches
    - ✓ Ureter
    - ✓ The Third branch of renal Artery
    - ✓ Lymph vessels and sympathetic also pass

#### Difference Between Right And Left Kidney

- ✓ The Right kidney is lower than left one
- ✓ Hilum of both kidneys are different from one another
- The upper poles are normally oriented more medially and posteriorly than the lower poles.
- ✓ Ascend of the kidney is prevented by IMA
- Left kidney is preferred for transplantation because it has a longer renal vein
- ✓ The Kidney receive 25% of cardiac output
- ✓ A single kidney show 5 segment



#### Pelations

Right	Left
Anterior  Right lobe of Liver  2 <sup>nd</sup> part of the duodenum  Suprarenal gland  Right colic flexure  Coil of the small intestine	Anterior  Spleen  Stomach and pancreas, lesser sac lies behind stomach and pancreas  Beginning of descending colon  Suprarenal gland  Ieft colic flexure  Coil of the jejunum
	Posterior

- Diaphragm
- Psoas muscle
- Quadratus lumborum muscle
- Transversus abdominis muscle
- Iliohypogastric and ilioinguinal nerve
- Costodiaphragmatic recess of pleura

#### Ureter

- 10 inch or 25 cm, the same length as of esophagus and duodenum, fallopian tube length is 10 cm
- The Ureter is Retroperitoneal structure
- The ureter enters the bladder at the upper lateral aspect of the base of the bladder
- It can be palpated through the lateral fornix of the vagina.
- The Ureter can't be palpated on per rectal examination
- it's not constricted at psoas muscle

#### 1) Constriction

- Uretero-pelvic junction—L2
  - ✓ It is the commonest site for congenital obstruction in urinary tract
  - ✓ The Upper part of the ureter is Supplied by renal artery.
- Pelvic brim/pelvic inlet:
  - ✓ Where it crossed by common iliac vessels
  - ✓ The Middle part of the ureter is Supplied by testicular artery/ovarian artery
- Uretero-vesical:
  - ✓ Turn antero-medialy open into the bladder at the level of Ischial spine
  - ✓ This is the narrowest part
  - ✓ Most common site for renal stone
  - ✓ The Lower part of the ureter is Supplied by superior vesical artery

#### 2) Histology:

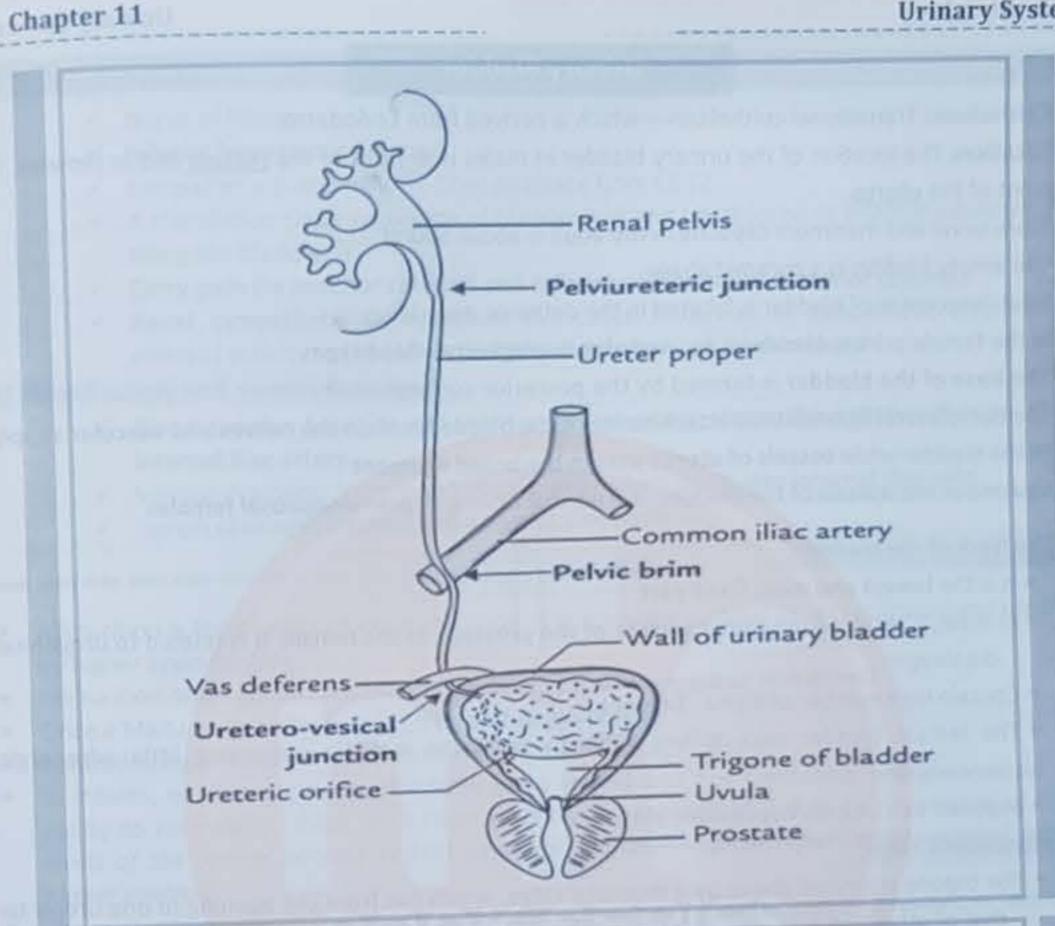
- Star-shaped small lumen
- Transitional epithelium
- No muscularis mucosa
- Inner longitudinal and outer circular smooth muscles

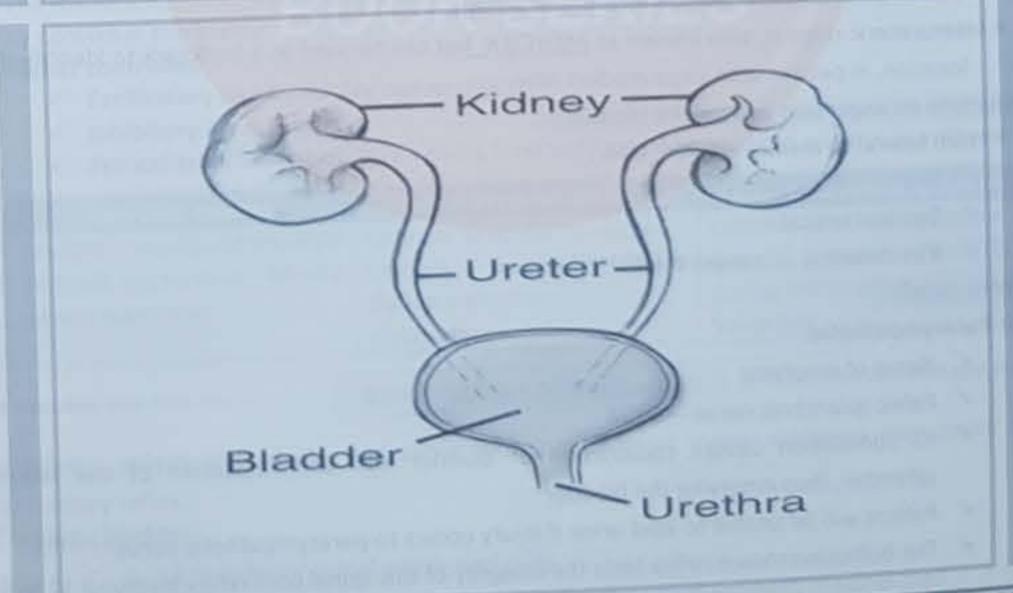
#### 3) Most common:

- . Most common site of injury: at the Pelvic brim during clamping of infundibulopelvit ligament
- Most common type of injury: obstruction
- Most common activity leading to injury: attempt to obtain hemostasis

#### 4) Relations:

- Anterior:
  - ✓ Testicular/ovarian vessels
  - ✓ Uterine artery
  - ✓ Duodenum is on right only
- Posterior
  - ✓ Common iliac artery bifurcation
  - ✓ Genitofemoral nerve





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#### Chapter 11

### **Urinary Bladder**

- Epithelium: Transitional epithelium--- which is derived from Endoderm
- Location: The location of the urinary bladder in males is in front of the rectum and in females, in front of the uterus.
- Store urine and maximum capacity in the adult is about 500ml
- The empty bladder is a pyramid shape
- Stretch receptor of bladder is located in the detrusor muscle
- in the female urinary bladder is located above urogenital diaphragm
- The base of the bladder is formed by the posterior surface
- The dorsolateral ligamentous attachments of the bladder contain the nerves and vascular supply to the bladder while vessels of uterus pass in the broad ligament
- Squamous metaplasia of the bladder is a normal finding in premenopausal females

### 1) The Neck of the bladder:

- . It is the lowest and most fixed part
- . In male, it rests on the upper surface of the prostate, in the female, it is related to urogenital diaphragm
- · Contain high number of alpha -1 receptor
- The female bladder neck differs strikingly from the male in possessing little adrenergic innervation.
- Supplied by L1-L2 via hypogastric plexus

### 2) Interureteric ridge:

- . The trigone is limited above by a muscular ridge, which run from the opening of one ureter to that of other and is known as Interureteric ridge.
- . Interureteric ridge is, also known as MERCIER bar can be used as a landmark to identify their location, in patient with large median lobe

### 3) Structure arrangement behind the bladder:

- . From lateral to medial include: USA
  - ✓ Ureter--most lateral
  - ✓ Seminal vesical
  - √ Vas deferens .....most medial

#### 4) Nerve supply:

### Parasympathetic:

- ✓ Nerve of emptying
- ✓ Pelvic splanchnic nerve—--S234
- ✓ Its stimulation causes constriction of bladder wall and relaxation of the Internal sphincter, thus emptying the bladder
- ✓ Patient will be unable to void urine if injury occurs to parasympathetic nerve
- The bulbocavernosus reflex tests the integrity of this spinal cord reflex involving S2 to 54.

#### Chapter 11

**Urinary System** 

#### Sympathetic:

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- ✓ Nerve of filling
- Inferior hypogastric plexus
- Sympathetic postganglionic fiber originate from L1-L2
- It stimulation cause relaxation of bladder wall and constriction of internal sphincter, thus filling the bladder
- √ Carry pain (to anterior column) and fullness sensation (to Posterior column)
- Renal sympathetic Denervation: this cause reduction of sympathetic afferent and efferent activity to the kidney and blood pressure can be decreased

#### 5) Blood supply and venous drainage:

- ✓ Blood supply—Superior and inferior vesical artery—from the anterior division of the internal iliac artery
- Venous drainage: Vein form vesical plexus which Drain into internal iliac vein
- Lymph drainage: internal and external iliac node

#### Micturation Reflex

- Micturition is the process of excreting urine. It is primarily a spinal reflex facilitated and inhibited by higher brain centers.
- Micturition reflex center: It is integrated in the sacral segment of spinal cord
- Once a Micturation reflex begins, it is "self-Regenerative"
- Controlled by mechanoreceptor in the bladder wall
- In infants, voiding occurs involuntarily (as a reflex) and not controlled by higher center. The ability to voluntarily inhibit micturition develops by the age of 2-3 years, as control at higher levels of the central nervous system develops. (Infant----spinal reflex) adult----spinal reflex +
- The micturition reflex is completely autonomic spinal cord reflex but can be inhibited or facilitated higher control) by centers in the brain.

#### Higher controlled:

- Facilitatory and inhibitory center: Pons
- ✓ Inhibitory area: Midbrain
- ✓ Frontal lobe: Send inhibitory signals, lesion of frontal lobe lead to urinary incontinence

Detrusor muscle	Internal urethral sphincter	External urethral sphincter
Smooth muscle/stimulated	Internal urethral sphincter - Smooth muscle/INHIBITED	External urethral sphincter  Skeletal muscle/INHIBITED  during micturition  Voluntary

### **Abnormalities of Micturition**

In infants, elderly individuals, and those with neurological injury, urination may occur as an involuntary reflex.

### 1) Spastic bladder:

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- ✓ Occur in anterior spinal artery occlusion
- ✓ Occur in the lesion of the spinal cord above the sacral segment of spinal cord

**Urinary System** 

- ✓ Present with—overactive bladder, urge incontinence
- ✓ Bladder contract which should not

#### 2) Atonic bladder:

- ✓ There is urine dribbling or Overflow incontinence
- Destruction of afferent (sensory) fibers from bladder prevent transmission of stretch signals from the bladder
- √ Causes:
- Lesion to the sacral part of the spinal cord during crash injury to the spinal cord
  - Cutting the autonomic afferent
  - O TABES DORSALIS
  - Sensory supply damage

#### 3) Neurogenic:

✓ Spastic or flaccid bladder

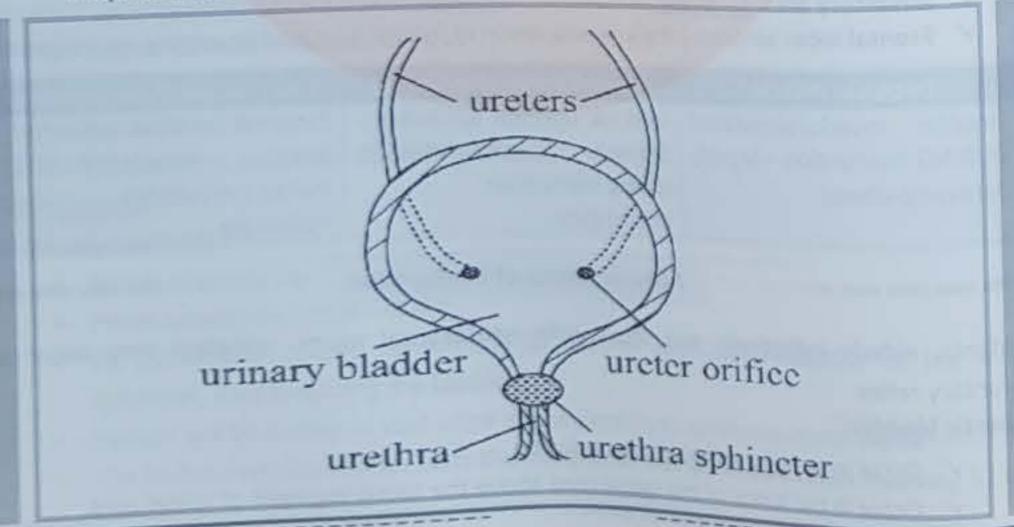
#### **Bladder Tumors**

#### Bladder carcinoma:

- Transitional cell carcinoma 90%
- Squamous cell carcinoma 5%
- Adenocarcinoma 2%

### Important risk factor for bladder carcinoma

- Cigarette Smoking (most common)
- Naphthalene (Aniline dye) factories (cause transitional carcinoma)
- Occupation (textile worker, dye worker, painters etc.)
- Schistosoma hematobium (cause Squamous Cell Carcinoma)
- Carcinoma bladder is associated with Kras gene
- · Carcinoma of the urinary bladder is the most common malignancy in Egyptians. At the national cancer institute in Cairo, it accounts for 27.6 of all cancer. This very high frequency is attributed to underlying Schistosomiasis



#### Urethra



#### .. The Female urethra is more prone to infection

Chapter 11

- . The female urethra is typically developed by the 12th gestational week.
- Somatic and autonomic nerves to the urethra travel on the lateral walls of the vagina near the urethra.

#### Parts of Urethra

#### 1) Prostatic urethra: Epithelium: Transitional epithelium/Urothelium

- ✓ It is the Widest and most dilatable portion of the urethra
- Ejaculatory duct enter at the posterior wall
- Midway along its length, the urethral crest is enlarged to form a somewhat circular elevation (the seminal colliculus). In men, the seminal colliculus is used to determine the position of the prostate gland during transurethral transection of the prostate.

#### 2) Membranous urethra: Epithelium: stratified / pseudostratified columnar epithelium

- ✓ The membranes urethra or intermediate urethra is the Shortest urethra
- ✓ It is the first site of resistance to be encountered on inserting catheter because it is the least distensible portion of the urethra.
- ✓ It is the 2<sup>nd</sup> most narrowest part of the urethra (first narrowest is external urethral meatus)
- ✓ Pass through the deep perineal pouch
- ✓ Most commonly injured following pelvic fracture
- 3) Bulbar urethra: Epithelium: stratified / pseudostratified columnar epithelium
  - ✓ Most commonly injured in trauma

#### 4) External urethral meatus:

- ✓ This is the Narrowest part of the male urethra
- 5) Sphincter urethra:
  - ✓ Supplied by the pudendal nerve

### Extravasation of urine in Injury of the urethra

Extravasation of urine refers to the condition where an interruption of the urethra leads to a collection of urine in other cavities such as the scrotum or the penis in males

### Membranous urethra rupture--- MUD

- ✓ Deep perineal pouch
- Prostatic urethra rupture---- PUS
  - ✓ Superficial perineal pouch

#### Penile urethra---PUS

✓ Superficial perineal pouch, As this pouch is closed on all sides except anteriorly, urine can only travel anteriorly to enter the scrotum deep to Dartos and then ascend in the anterior abdominal wall.

#### Bulbar urethra rupture: BUS

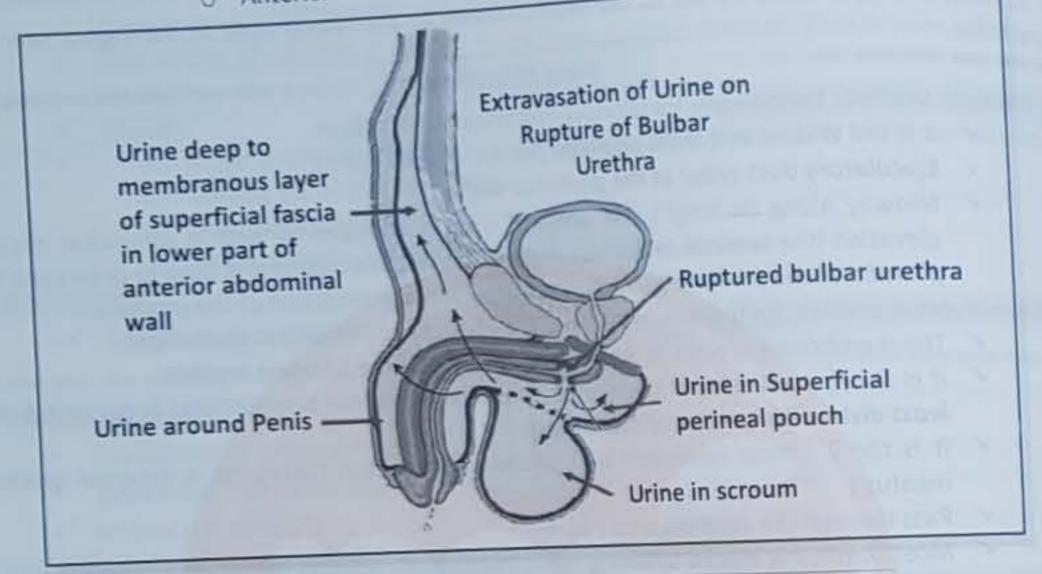
- ✓ Most commonly injured by falling on projecting object, bicycle, and fall in manhole
- In Intact Buck's fascia urine will confined into the penis

#### Chapter 11

**Urinary System** 

# ✓ In Rupture buck's fascia, extravasations will occur first into

- Superficial perineal pouch—First
  - o Scrotum-Second
  - Anterior abdominal wall—Third



#### **Clinical Points**

### In the male, the histology of cancer:

- In the prostatic urethra is the transitional cell in 90% and squamous cell carcinoma in 10%;
- In the penile urethra, 90% are squamous cell cancers and 10% are transitional cell tumors;
- And in the bulbomemebranous urethra 80% are squamous cell, 10% are transitional cell and 10% are Adenocarcinoma. In the female, squamous cell carcinoma accounts for one third, Adenocarcinoma for one third, and transitional cell carcinoma for one third.
- Adenocarcinoma is the most common type of tumor to occur in a urethral diverticulum.
- . In the male, the anterior urethra lymphatics drain to the inguinal nodes, and the posterior ureth lymphatics drain to the pelvic nodes.
- . In the female, the anterior urethra (distal third) lymphatics drain to the inguinal nodes. The posterior urethra lymphatics (proximal two thirds) drain to the external and internal iliac and obturator lymph nodes.
- . Lesions associated with the development of penile cancer include cutaneous hor balanitisxerotica obliterans, and pseudoepitheliomatousmicaceous and keratoticbalanitis. The most important risk factor for penile cancer is infection with HPV
- Carcinoma in situ of the glans is called erythroplasia of Queyrat; if carcinoma in situ is on the shaft of the penis it is called Bowen disease.
- Penile tumors may present anywhere on the penis but occur most commonly on the Glans (48) and prepuce (21%).
- The most common injured structure in pelvic fracture is urethras.

### Development of the Urinary System



. The urogenital system develops from:

- The Intermediate mesoderm
- The mesodermal epithelium (Mesothelium) of the peritoneal cavity,
- and the endoderm of the urogenital sinus
- . The intermediate mesoderm used to lie lateral to the somites, then moved away from the somites during the lateral folding. It forms the urogenital ridge which is comprised of:
  - A Nephrogenic cord or ridge
  - And a Gonadal or genital ridge

#### 3 Successive Sets of kidneys development:

#### 1. Pronephros:

S S S X X

 The nonfunctional, rudimentary Pronephros develops early in week 4. But they degenerate, leaving behind the pronephric ducts which run to the cloaca. These ducts will remain for other kidneys.

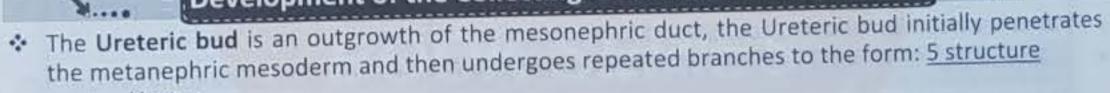
#### 2. Mesonephros:

The Mesonephros develop later during week 4, serving as temporary excretory organs.

#### 3. Metanephros:

- This is the caudal-most nephritic structure.
- The functional Metanephros or permanent kidneys develop early in week 5 and functional in the fetus at about week 10 and excrete urine into the amniotic fluid
- This excretion continues during fetal life and the fetus swallows this urine mixed in the amniotic fluid. It is then absorbed in the stomach and duodenum to the blood for transport to the placenta and disposal.

### Development of the Collecting Ducts and Urinary Bladder



- Ureter
- Renal pelvis, Major calyces,
- Minor calyces
- Collecting ducts
- . The metanephric diverticulum or Ureteric bud penetrates the metanephric mesoderm in the caudal part of the nephrogenic cord and stimulates the formation of the metanephric mass or cap. The metanephric mesoderm gives rise to the Nephrons:
  - Glomerulus,
  - Bowman's capsule,
  - Proximal convoluted tubule,
  - Loop of Henle and Distal convoluted tubule
  - The cortex of the kidney in the newborn contains mostly undifferentiated mesenchyme; the Nephrons continue to develop several months after birth.
- The urinary bladder develops from the urogenital sinus and the surrounding splanchnic mesenchyme. The urogenital sinus is comprised of 3 regions:
  - The cranial or vesical region:
    - ✓ Which will form the bladder and which is attached to the Allantois.
    - ✓ After birth, the Allantois degenerates and becomes the Urachus forming the median umbilical ligament.

## Urinary System

- The transitional epithelium of the bladder develops from the endoderm of the
- The middle or pelvic region: Main part of the male urethra(prostatic and membranous part) and entire female urethra, prostate is formed by the bud from the prostatic urethra
- The caudal or phallic region: phallic part grows towards genital tubercle

#### Clinical Consideration:

- Incomplete division of the metanephric diverticulum or Ureteric bud results in the double ureter and supernumerary kidney
- Failure of the kidney to "ascend" from its embryonic position in the pelvis results in an ectopic kidney that is abnormally rotated
- If renal agenesis or urethral obstruction occurs, oligohydramnios results
- If esophageal or duodenal atresia occurs, then polyhydramnios results
- Supernumerary renal arteries (two or more arteries to a single kidney) are the most common renovascular anomaly, occurrence ranging from 25% to 40% of kidneys
- Renal agenesis: failure of the Ureteric bud to penetrate the metanephrogenic blastema result in failure of kidney development. absence of Ureteric bud leads to renal agenesis.

#### **High-Yield Points**



- The medial aspect of each kidney is rotated anteriorly 30 degrees.
- The 12th rib overlies the right kidney; the 11th and 12th ribs overlie the left kidney.
- The columns of Bertin contain the interlobar arteries.
- Renal hilar structures from anterior to posterior are renal vein, renal artery, and renal pelvis.
- . The line of Brodel is an avascular plane between the anterior and posterior segments. It is variable in location and must be defined for each individual kidney
- Lumbar veins may drain directly into the renal veins, which occurs more commonly on the left. They may be the source of troublesome bleeding when dissecting around the renal vein.
- Gerota fascia encasing the kidneys, adrenal glands, and abdominal ureters is closed superiorly and laterally and serves as an anatomic barrier to the spread of malignancy as well as a means of containing perinephric fluid collections. Superiorly, the Gerota fascia is continuous with the diaphragmatic fascia on the inferior surface of the diaphragm, whereas inferiorly, the anterior and posterior layers of Gerota fascia are loosely attached where perinephric fluid collections can track inferiorly into the pelvis without violating Gerota fascia,
- Each renal artery divides into five segmental end arteries that do not anastomose significantly with other segmental arteries. They are end arteries and, when occluded, cause renal tissue ischemia and tissue atrophy.
- The blood supply of the ureter is medially in the proximal part, posteriorly in the mid-portion, and laterally in the distal portion
- The posterior segmental artery represent the first and most constant branch, which separate from the renal artery before it enter the renal hilum
- the renal artery before it critically the the INTER-LOBULAR orteries which then supply the glomeruli via the afferent arterioles

#### CHAPTER

## RENAL PHYSIOLOGY & PATHOLOGY

### PHYSIOLOGY

#### **Body Fluids**

#### **Total Body Water (TBW)**

- = In the average young adult male, 18% of the body weight is protein and related substances, 7% is mineral, and 15% is fat. The remaining 60% is water.
- Total body water in 70kg------40L
- TBW lowest in-----Adult females
- TBW highest in----newborn, infant (75%) and adult males
- Marker to measure volume---Titrated H2O, D2O, antipyrine
- In severe dehydration, Total body water decreases

#### Intracellular Fluid (ICF)

Slightly Acidic to ECF

0.000

- 2/3 or 40% or of TBW
- Major cation: K<sup>+</sup> and mg<sup>+</sup> 98% of K<sup>+</sup> in cell
- Major anion: protein and organic phosphate
- ICF = TBW-ECF
- Buffer---Protein
- Water enters into cells through pores
- A worker sweats 2L & drink 2L of pure water will cause Increase in ICF
- A women run a marathon in 90 °F weather and replace all volume lost in sweat by drinking distilled water, after marathon, she will have decrease plasma Osmolarity

#### Extracellular Fluid (ECF)

- 20% or 1/3<sup>rd</sup> of TBW
- Marker: SIM: Sulfate, Inulin, Mannitol
- Buffer: HCO3
- Provide nutrient to the cell, pH---7.4
- Primary dehydration cause ECF to become hypertonic

### Interstitial Fluid

- 3/4<sup>th</sup>-----15%
- Also called 3<sup>rd</sup> space
- Fluid loss from 3<sup>rd</sup> space should be replaced by R/L
- Ultrafiltratable plasma
  - Same as plasma except low protein
  - Buffer----HCO3
  - Interstitial fluid = ECFplasma volume

#### Plasma-

- = 1/4<sup>th</sup>----5%
- Difference between plasma and interstitial fluid is 1mosml
- Highest protein content
- of Marker: RISA, Evans blue
  - . The composition of the intestinal fluid is the closest to that of plasma

Various types of Fluid and Clinical Points

- Oliguria-----urine output---- < 500ml/day or <0.5ml/kg/hr
- Anuria----<50ml/day
- In CRF fluid restriction------0.5 L/day

NAME AND POST OFFICE ADDRESS OF THE OWNER.

- The minimum amount of urine required to remove metabolic waste is -500-600ml
- A normal adult pass 1000 to 1500ml urine per day
- Water intoxication sign------Slow pulse
- A person suffering from dehydration-----replacement of Na is most important
- Compared with the person who ingests 2L of distilled water, a person with water deprivation will have a-----higher rate of H2O reabsorption in collecting duct, the person with water deprivation will have higher plasma Osmolarity and higher circulating level of ADH. These effects will increase the rate of H<sub>2</sub>O reabsorption in the collecting ducts and create negative free water clearance
- Sodium: Sodium ions outnumber any other cations in the ECF; therefore it is essential in the fluid regulation of the body.
- Potassium: The ECF has a low concentration of potassium and can tolerate only small changes in its concentrations.

#### Normal Saline

- Physiologic saline is a 0.9%s solution of NaCL and is also called normal saline. It is also called isotonic saline because it has an Osmolarity of 308 mOsm/L
- I/V Fluid of choice for Paradoxical aciduria -----Normal saline
- After infusion of N/S-----blood volume increase---because N/S is isotonic and that's why cause isosmotic volume expansion
- Human plasma is the same as 0.9% N/S, Normal saline has an osmolality close to that of plasma.
- A normal saline solution is the 0.85% sodium chloride solution, that means that 0.85gm of sodium chloride in 100ml distilled water, to convert gm into mg, multiply it with 1000 so 0.85 x1000/100= 850mg/100ml
- Normal saline is 0.9% saline. This means that there is 0.9 G of salt (NaCl) per 100 ml of solution, of 9 G per liter
- Isotonic solution: will raise ECF volume but not change serum sodium concentration e.g. 0.9% N/S, 5% dextrose in water, ringer solution
- Hypertonic solution: will raise ECF volume and increase serum sodium concentration e.g. 3% Nacl, 5% Nacl, 3% Nacl or 5% Nacl + dextrose water
- Hypotonic solution: will raise ECF volume and decrease serum sodium concentration e.g. 0.45% Nacl, 0.33% Nacl, 0.2% Nacl, 2.5% dextrose water

#### Ringer lactate and dextrose water

- I/V fluid of choice for blood loss and dehydration is Ringer lactate
- Administering dextrose 5% is equivalent to administering pure water because the dextrose metabolized to carbon dioxide and water. Distilled water = Pure water
- metabolized to carbon dismission: NaCl, lactate, K' and Ca" but having no magnesium

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Renal Physiology and Pathology

#### Plasma Osmolarity and Urine Osmolarity

- SIADH can be differentiated from severe dehydration by plasma Osmolarity, in SIADH plasma Osmolarity must be low while in severe dehydration plasma Osmolarity can be normal, urine Osmolarity is increase in both cases
- In human, serum Osmolarity is primarily determined by serum sodium concentration, since this the most abundant differentially permeable membrane present in serum
- \* ADH is responsible for the regulation of water excretion by the kidney
- Aldosterone regulates sodium excretion in the distal tubules and collecting duct
- . Angiotensin-II has the net effect of increasing sodium and water retention via the following mechanism:
  - Stimulation of Aldosterone secretion
  - Direct stimulation of renal tubular Na<sup>†</sup> reabsorption
  - Stimulation of ADH and thirst

#### 1) Serum Osmolarity

- The reference range of serum Osmolarity is 275-295mosm/kg
- Increase in ------Water deprivation, central and nephrogenic Diabetes insipidus
- Decrease in-----SIADH and injection of ADH---means more ADH

#### 2) Urine Osmolarity:

- Increase in-----SIADH
- Decrease in------Diabetes insipidus, excess fluid intake
- Question: Serum Osmolarity is 300mosm/L and Urine Osmolarity is 1200 mosm/L, what is the cause. The cause of this low serum Osmolarity (250mosm/L) is and high urine Osmolarity (1200 mosm/L) is SIADH

#### 3) Isosmotic volume expansion:

- ECF volume increase, but no change occurs in the Osmolarity of ECF or ICF
- Example: infusion of isotonic NaCl

#### 4) Isosmotic volume contraction

- ECF volume decrease, but no change occurs in the Osmolarity of ECF or ICF
- Example: Diarrhea

#### 5) Hyper-osmotic volume expansion

- The Osmolarity of ECF increases because osmoles(NaCl) have been added to the ECF
- ECF volume increase and ICF volume decrease
- Example: Excessive NaCl intake

#### 6) Hyper-osmotic volume contraction

- The Osmolarity of ECF increase
- ECF volume decrease
- Example: sweating in desert, diabetes insipidus and fever

#### 7) Hyposmotic volume expansion

- The Osmolarity of ECF decrease
- ECF volume increase
- Example: SIADH

### 8) Hyposmotic volume contraction:

- The Osmolarity of ECF decrease
- ECF volume decrease
- Example: adrenal insufficiency

Renal Physiology and Pathology

# Glomerular Filtration Rate (GFR) and Creatinine

# Best way to measure renal/plasma flow-------Para-aminohippurate (PAH) clearance

- Substances which has the highest renal clearance----------PAH-------because it both filtered
- and secreted. Inulin is only filtered.

#### Creatinine

- ❖ The Best way of Measurement of GFR———Clearance of Inulin
- The Best way of Estimation of GFR————Creatinine clearance
- Clinically GFR is measured by------Creatinine clearance
- The most sensitive test to asses renal failure is———Creatinine clearance
- Creatinine is a non-protein nitrogenous compound that is produced by the breakdown of creatine in muscle. 98% of creatine are present in skeletal and heart muscle
- . Creatinine is found in serum, plasma, and urine and is excreted by glomerular filtration at a constant rate and in the same concentration as in plasma.
- . Creatine and creatinine are not the same things. Creatine is found in the muscle. Creatinine is a breakdown products of creatine phosphate
- . The creatinine is a waste product of creatine phosphate and it will be excreted by the kidney in the urine at the rate of 1-2 g/day
- Serum creatinine level is an important diagnostic tool to asses renal function
- . The most accurate and practical assessment of renal function for routine use after Nephrectomy is serum creatinine-based estimation of GFR, such as CKD-EPI formula.

#### Glomerular filtration rate (GFR)

NAME AND ADDRESS OF THE OWNER, WHEN PERSON NAMED IN GFR normally is about 180 L/day, tubular reabsorption is 178.5 L/day, and urine excretion is 1.5 L/day

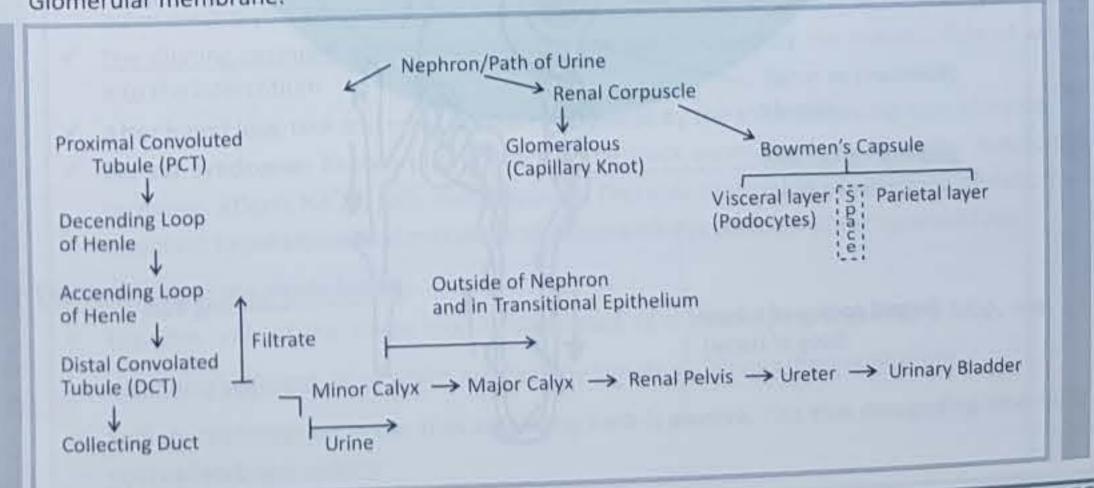
- Increase in GFR by:
  - ✓ Constriction of Efferent arteriole
  - Decrease Afferent arteriole resistance
  - Afferent arteriole dilation
  - ✓ Increased Glomerular Capillary Filtration Coefficient Increases GFR
  - ✓ Increased Glomerular Capillary Hydrostatic Pressure Increases GFR
- O Decrease GFR by:
  - ✓ Afferent arteriole constriction
  - ✓ Increased Bowman's Capsule Hydrostatic Pressure
  - ✓ Increased Glomerular Capillary Colloid Osmotic Pressure Decreases GFR
- Effects of sympathetic NS on renal blood flow and GFR:
  - ✓ Slight to moderate stimulation have only mild effect in decreasing RBF and GFR
  - ✓ Strong acute stimulation constrict renal arterioles and decrease RBF and GFR
  - ✓ If sympathetic stimulation is continued, RBF, GFR and urine output come to normal within 20-30min
- O Plasma clearance is maximum for: PAKI-UNiversity
  - ✓ PAH
  - K+
  - Inulin
  - ✓ Urea

Chapter 12

Renal Physiology and Pathology

#### Nephrons

- Each individual renal tubule and its glomerulus is a unit (nephron).
- The size of the kidneys between species varies, as does the number of nephrons they contain.
- . Each human kidney has approximately 1.3 million nephrons.
- \* The glomerulus, which is about 200 µm in diameter, is formed by the invagination of a tuft of capillaries into the dilated, blind end of the nephron (Bowman's capsule).
- . The capillaries are supplied by an afferent arteriole and drained by a slightly smaller efferent arteriole, and it is from the glomerulus that the filtrate is formed.
- \* Two cellular layers separate the blood from the glomerular filtrate in Bowman's capsule: the capillary endothelium and the specialized epithelium of the capsule. The endothelium of the glomerular capillaries is fenestrated, with pores that are 70 to 90 nm in diameter. The endothelium of the glomerular capillaries is completely surrounded by the glomerular basement membrane along with specialized cells called podocytes.
- . Podocytes have numerous pseudopodia that interdigitate to form filtration slits along the capillary wall. The slits are approximately 25 nm wide, and each is closed by a thin membrane. The glomerular basement membrane, the basal lamina, does not contain visible gaps or pores.
- Stellate cells called mesangial cells are located between the basal lamina and the endothelium. They are similar to cells called pericytes, which are found in the walls of capillaries elsewhere in the body.
- Functionally, the glomerular membrane permits the free passage of neutral substances up to 4 nm in diameter and almost totally excludes those with diameters greater than 8 nm. However, the charges on molecules as well as their diameters affect their passage into Bowman's capsule. The total area of glomerular capillary endothelium across which filtration occurs in humans is about 0.8 m<sup>2</sup>
- . The basement membrane has an overall negative charge due to presence of Sialic Acid in the Glomerular membrane.

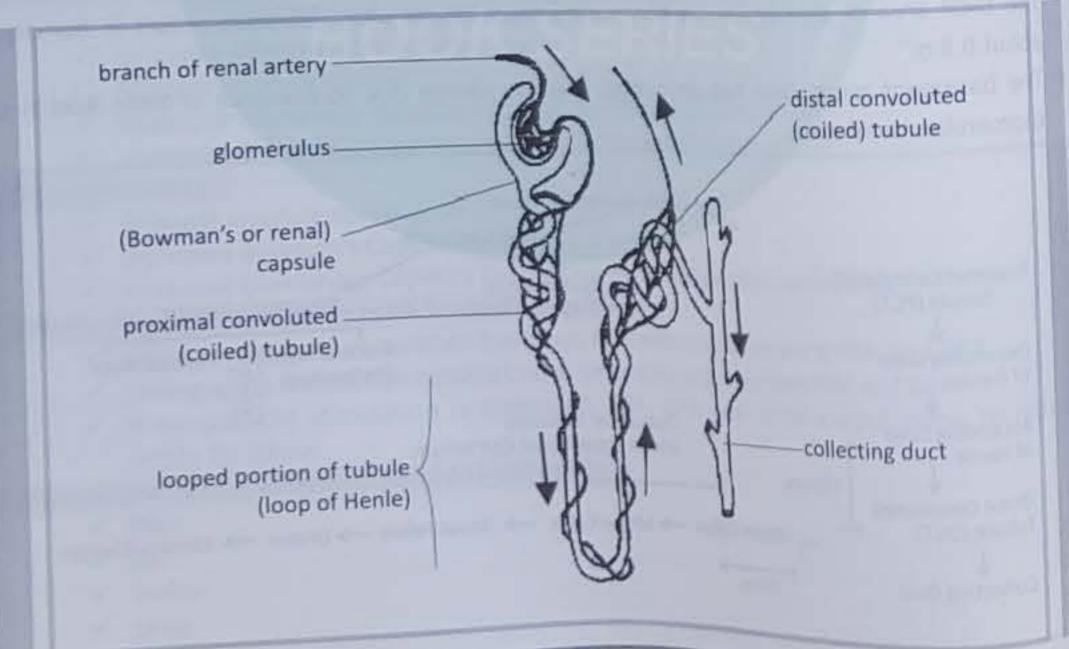


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Renal Physiology and Pathology

Proximal Convoluted Tubules- PCT

- The human proximal convoluted tubule is about 15 mm long and 55 μm in diameter
- Longest and most Tortous part of renal tubules
- . Early PCT is the "workhouse" of the Nephrons
- ❖ The Tubular fluid is isosmotic to plasma in proximal tubules with Osmolarity of 300 mOsm/L
- Increase GFR cause increase absorption of salt and water from PCT
- \* Reabsorb 2/3rd or 60% of the filtered Na and water, in presence or absence of ADH greatest fraction of the fluid will be absorbed from PCT which is 2/3 or 60% of filtered water
- ❖ Na<sup>+</sup> is reabsorbed by cotransport with, maximum glucose absorption occurs in PCT
- Carbonic anhydrase inhibitors and osmotic diuretic act on PCT
- Alpha-1 hydroxylase activation occurs in PCT
- PTH inhibits phosphate reabsorption in PCT by cAMP
- 67% of K+ absorb In PCT
- \* Acute renal failure most commonly affect PCT, this part is very prone to ischemia
- \* Actively reabsorbed substance: Na<sup>+</sup>, K<sup>+</sup>, glucose, Amino acid, Uric acid, Vit C and lactic acid
- Passively Reabsorbed Substances: Cl , H<sub>2</sub>O, CO<sub>2</sub>, urea and protein
- Substances Actively Secreted: H<sup>+</sup>, organic acid and Bases
- Fanconi syndrome:
  - ✓ Generalized reabsorption defect in PCT.
  - ✓ Associated with increase excretion of nearly all amino acid, glucose (Glycosuria with normal blood glucose), HCO3, and PO43 (hypophosphatemia, rickets). K+ (hypokalemia).
  - ✓ May result in metabolic acidosis (proximal renal tubular acidosis).



#### **Loop of Henle**

- . Both thick and thin ascending loop is virtually impermeable to water
- . Tip of loop Henle----increase Osmolarity
- . Countercurrent multiplication in the loop of Henle depends on NaCl reabsorption in the thick ascending limb and countercurrent flow in the descending and ascending limbs of the loop of Henle

#### (1) Thick Descending limb of the Henle loop

- ✓ The descending limb of Henle loop Is also known as the straight portion (pars recta)of the proximal tubules
- ✓ It is lined by a simple Cuboidal epithelium that has a prominent brush border and is similar to that lining of PCT
- ✓ Its function is to resorb, exchange, and excrete in a manner similar to that of the PCT

#### Thick Ascending Loop of Henle (TAL):

- ✓ The ascending thick limb of Henle is also known as the straight portion (Pars recta) of the distal tubules
- ✓ Lined by Simple Cuboidal epithelium
- ✓ It establishes a gradient of Osmolarity in the medulla
- ✓ In the TAL sodium reabsorption is active via the NKCC2 transporter on the apical membrane. This transporter moves one sodium ion, one potassium ion and two chloride ions across the apical membrane.
- ✓ It is the site of action for loop diuretic (such as Furosemide)
- ✓ Impermeable to water, even in the presence of a large amount of ADH. As the sodium and other electrolytes are reabsorbed from the ascending limb, its filtrate becomes hypotonic
- The diluting segment, solutes pumped out are not followed by the osmotic flow of water into the interstitium
- ✓ After blood loss, GFR and urine output is increased by the thick ascending loop of Henle
- ✓ Bartter syndrome: Reabsorption defect in the thick ascending loop of Henle. Autosomal recessive. Affects NA<sup>+</sup>/K<sup>+</sup>/2CL<sup>-</sup> cotransporter. Presents similarly to chronic loop diuretic use. Results in hypokalemia and metabolic alkalosis with Hypocalcemia and hypercalciuria

### The Thin limb of the Henle loop:

- ✓ The thin limb of the Henle loop is composed of a descending segment, a loop, and an ascending segment, all of which are lined by Simple squamous (flat) epithelium
- ✓ Sodium reabsorption in the thin ascending limb is passive. The thin descending limb does not reabsorb any sodium

# Distal Convoluted Tubules-DCT

- The distal convoluted tubule, which starts at the macula densa, is about 5 mm long.
- Its epithelium is lower than that of the proximal tubule, and although a few microvilli are present there is no distinct brush border. The distal tubules coalesce to form collecting ducts that are about 20 mm long and pass through the renal cortex and medulla to empty into the pelvis of the kidney at the apexes of the medullary pyramids. The epithelium of the collecting ducts is made up of principal cells (P cells) and intercalated cells (I cells). The P cells, which predominate, are relatively tall and have few organelles. They are involved in Na<sup>+</sup> reabsorption and vasopressinstimulated water reabsorption. The I cells, which are present in smaller numbers and are also found in the distal tubules, have more microvilli, cytoplasmic vesicles, and mitochondria. They are concerned with acid secretion and HCO3 transport. The total length of the nephrons, including the collecting ducts, ranges from 45 to 65 mm.
  - \* The distal convoluted tubule is continuous with macula densa. Histologically, similar to thick ascending limb of loop of Henle
  - Impermeable to water
  - \* DCT modifies its lining cell
  - \* Regardless of whether ADH present or absent, fluid leaving the early distal tubular segment is hypo-osmotic with an Osmolarity of only about one third the Osmolarity of plasma
  - ❖ PTH increases calcium reabsorption by activating adenylate cyclase in the distal tubules
  - . Loop and thiazide diuretic work synergistically at DCT
  - (5) Early distal tubules:
    - ✓ The area of the Nephron with the lowest Osmolarity will the early distal tubules, a Nephron-diluting segment
    - ✓ Impermeable to water
    - ✓ It is the site of action for thiazide diuretics.
  - (3) Late distal tubules:
    - ✓ ADH increase the permeability of the principle cells of the late distal tubules
    - ✓ It is the site of action for potassium-sparing diuretics (Spironolactone, triamterene,
  - Gitelman syndrome: Reabsorptive defect of NaCl in DCT. Similar to using lifelong thiazide diuretic An Autosomal recessive disease. Lead to hypokalemia, hypomagnesemia, metabolic alkalosis with hypercalciuria

Changes in Di	stal K <sup>†</sup> secretion
Causes of Increased distal K <sup>†</sup> Secretion	Causes of Decreased distal K <sup>+</sup> secretion
<ul> <li>Higher-K+ diet</li> <li>Alkalosis</li> <li>Thiazide and loop diuretics</li> <li>Hyperaldosteronism</li> <li>Luminal anions</li> </ul>	<ul> <li>Lower-K+ diet</li> <li>Acidosis</li> <li>K* sparing diuretics</li> <li>Hypoaldosteronism</li> </ul>

Chapter 12

STREET, STREET

Renal Physiology and Pathology

#### **Potassium Shifts**

Shift K* into cell/cause hypokalemia	Shift K <sup>+</sup> out of cell/Cause hyperkalemia
<ul> <li>Hypo-Osmolarity</li> <li>Alkalosis</li> <li>B-adrenergic Agonist</li> <li>Insulin administration</li> </ul>	<ul> <li>Hyper-Osmolarity</li> <li>Acidosis</li> <li>B-blocker, digitalis</li> <li>High blood sugar (insulin deficiency)</li> <li>Strenuous Exercise</li> <li>Cell lysis e.g. crush injury, rhabdomyolysis</li> <li>Succinylcholine (increase risk in burns/muscle trauma)</li> </ul>

### Collecting Duct (CD)

- The collecting duct balance the water concentration of the blood through hormonal control
- · Epithelium: Simple Cuboidal cells
- Lies in Medullary rays
- As in the late distal tubules, ADH increase the permeability of the principles cell of the collecting
- . If a person is dehydrated, ADH act on the wall of the collecting duct, producing aquaporins (channels), making it more permeable to water. More water is transferred into the blood. Urine output becomes hypertonic

## Juxtaglomerular Complex/Apparatus (JG Apparatus)

- Juxtaglomerular apparatus is located at the angle of the afferent and efferent arterioles where it comes in contact with cortical thick ascending limb
- Lies at vascular pole of the renal corpuscle
- Composed of:
  - ✓ Macular densa----this is the modified region of the tubular epithelium. It marks the
  - ✓ JG cell-----these are Modified muscle cells in the tunica media of the afferent arteriole. These cells have renin-containing granules
  - ✓ Mesangial cell: Lies in between afferent and efferent arteriole
- Macula densa (DCT)-----Sense Osmolarity of fluid in DCT-----cause release of renin
- ❖ JG cells------Sense decrease BP-----release renin (renin release increase by the decrease in ECF volume)
- ----Receptors for angiotensin II and ANP
- \* Histology of macula densa: The cells of the macula densa are taller columnar and have more prominent nuclei than surrounding cells of the distal straight tubule
- (3) JG cell tumor:
  - ✓ Almost all patients have hypertension that is difficult to control.
  - ✓ Other symptoms reported include pain, headache, polyuria, Nocturia, dizziness, and vomiting. Other typical clinical findings include high serum renin levels, elevated serum Aldosterone, and hypokalemia Page | 341

Renal Physiology and Pathology

# Difference between Cortical and Juxta- Medullary Nephron

### ✓ Cortical Nephrons:

- o Form 85% of the Nephrons
- o Short loop of Henle
- o Blood flow is large
- o Peritubular capillary network is short
- O O2 extraction is very less

### ✓ Juxtamedullary Nephrons:

- o Form 15% of the Nephrons
- o long loop of Henle
- o Blood flow is less
- o Form vasa recta
- o O2 extraction is very large

# Agents causing contraction and relaxation of mesangial cells:

### Contraction:

- Endothelins
- Angiotensin II and Vasopressin
- o Nor-epinephrine
- Platelet activate factor
- Platelet-derived growth factors
- Thromboxanes A2
- o Histamine
- O LT-Ca and Da PGF

#### ✓ Relaxation:

- o ANP and Dopamine
- o PGE2
- o campa

### Renal System Histology

- -Fenestrated epithelium Glomerulus-
- -Epithelium with two layers, visceral layer and the parietal layer Bowman capsule-
- -Simple Cuboidal epithelium with brush border Proximal convoluted tubules-
- -Thick segment consist of simple Cuboidal epithelium, thin Loop of Henlesegment consists of Simple squamous (flat)epithelium
- -Simple Cuboidal epithelium without a brush border Distal convoluted tubules-
- -Simple Cuboidal epithelium Collecting tubules-
- -- Simple columnar epithelium Collecting duct-
- -Transitional Epithelium Renal calyces--Transitional Epithelium
- Renal pelvis--Transitional Epithelium
- --- Transitional epithelium/Urothelium Prostatic urethra----
- Prostatic urethra—————————————————————Stratified / pseudostratified columnar epithelium

### Free water clearance (CH20)

- . Is used to estimate the ability to concentrate or dilute the urine
- Free water or solute-free water, is produced in the diluting segment of the kidney
- . In the absence of ADH, this solute free water is excreted and CH20 Is positive
- In the presence of ADH, this solute free water is not excreted but is reabsorbed by the late distal tubules and collecting ducts and CH20 Is negative
- CHZO Is zero (urine that is isosmotic to plasma): is produced during treatment with a loop diuretic
- \* CHZO Is positive (urine that is Hyposmotic to plasma-----low ADH): is Produced by high water intake, central diabetes insipidus or nephrogenic diabetes insipidus
- CHZO Is negative (urine that is hyperosmotic to plasma-----high ADH): Produced in water deprivation or SIADH
- Hyponatremia: <130mEq/I</li>
  - Mild asymptomatic Hyponatremia: treatment; Fluid restriction
  - Hyponatremia + CNS symptoms: treatment; hypertonic saline
  - Rapid correction of Hyponatremia >1-2 mEq/L can lead to central pontine myelinolysis

### **Glucose Clearance**

- Tubular transport maximum: tubular transport maximum or Tm is the rate at which the maximum amount of substance is reabsorbed from the renal tubules. Every substances having Tm value has also a threshold level in plasma or blood. Below that threshold level, the substances is completely reabsorbed and does not appear in the urine
- Glucose at a normal plasma level (range 60-120mg/dl) is completely reabsorbed in PCT by Na\*/glucose cotransport
- In the adult, at plasma glucose of 200mg/dl glucosuria begins (threshold)
- At the rate of 375mg/min all transporter are fully saturated (T<sub>m</sub>)
- · Splay: -----is the region of the glucose curves between threshold and Tm, occurs between plasma glucose concentration approximately 250 and 350 mg/dl
- The Normal pregnancy may decrease the ability of PCT to reabsorb glucose and amino acids----glucosuria, an aminoaciduria
- · Simple: Renal threshold for glucose is 200mg/dl, the renal threshold for glucose in arterial is 200mg/dl renal threshold for glucose in venous blood is 180mg/dl
- Glucose will be detected in the urine when the serum level is above 180mg/dl (from Campbell-Walsh urology 11th editions)

### **Major Buffers**

- ----HCO3 (Bicarbonate buffer system) \* Body/ECF (interstitial fluid)/blood----is the most powerful extracellular buffer system of the body
- ❖ ICF———Protein
- is not far from the normal pH of 7.4 in the body fluids
- ------So Hb is the intracellular buffer

- Most cases of renal artery stenosis are asymptomatic, and the main problem is high blood pressure that cannot be controlled with medication
- Example: A 60-year-old patient presented with high Blood pressure. Lab investigation reveals an increase in plasma renin activity. Left renal vein, renin is high and his <u>right renal vein renin level</u> is <u>decreased</u>. The diagnosis in this case is the left renal artery stenosis
- Angiotensin-converting enzyme inhibitors (ACEIs) are contraindicated in patients with bilateral renal artery stenosis due to the risk of azotemia resulting from preferential efferent arteriolar vasodilation in the renal glomerulus due to inhibition of angiotensin II.

### Regulation of Arterial Pressure

- Rapidly- acting pressure controlling mechanism-i.e. Nervous mechanism acting within second or minutes e.g.
  - ✓ Baroreceptor feedback mechanism:
    - Rapid, first line, quick mechanism
    - o 60-200 mmHg range of BP
  - ✓ CN5 ischemic response:
    - One of the most powerful and most potent activators of the sympathetic vasoconstrictor system
    - Activated only at 60 mmHg or below
    - Emergency pressure control system
  - ✓ Chemoreceptor mechanism
  - ✓ Atrial and pulmonary artery reflex
  - ✓ Bainbridge reflex
  - ✓ Abdominal compression reflex
- Intermediate time-period pressure control mechanism: acting within minute or hours e.g.
  - ✓ Renin-angiotensin vasoconstrictor mechanism
  - ✓ Stress relaxation mechanism
  - ✓ The capillary fluid shift mechanism
- Long-term pressure control mechanisms: Acting within days, months or years e.g.
  - ✓ Renal body fluid mechanism
  - ✓ Renin-angiotensin Aldosterone mechanism

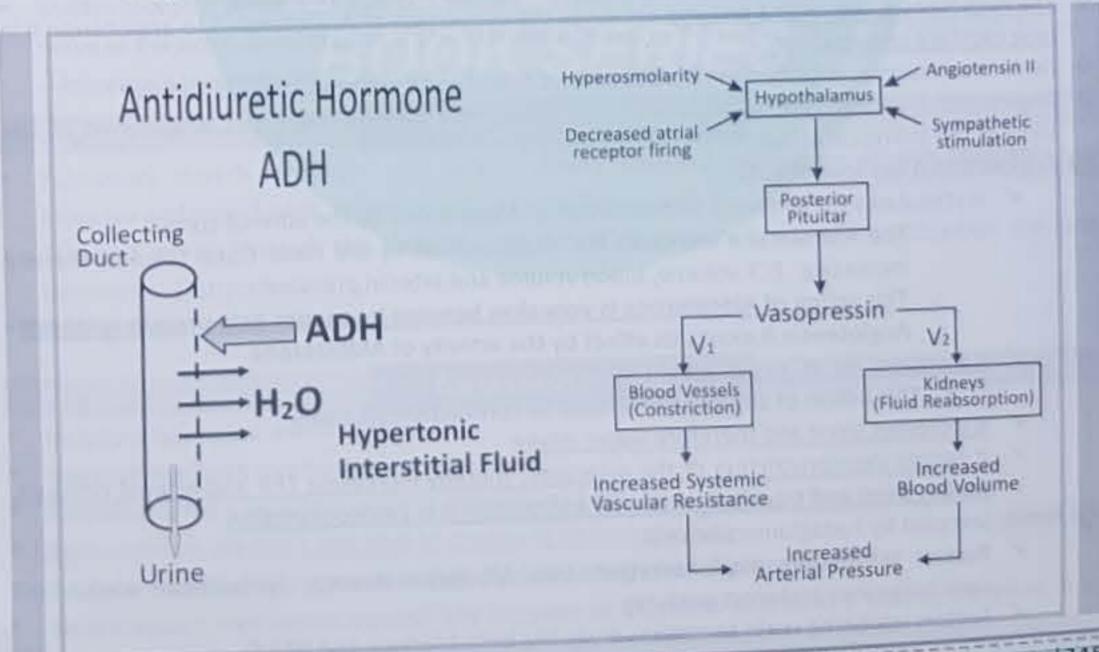
Chapter 12

Renal Physiology and Pathology

### IMPORTANT HORMONES

#### ADH

- Act on collecting duct(CD) and late distal tubules(DT) but CD>DT
- Regulate serum Osmolarity by increasing only H20 (pure water no sodium) Permeability
- ADH has the greatest effect on plasma Osmolarity
- . In presence of ADH filtrate will be isotonic to plasma in Cortical collecting tubule
- . The major function of ADH is Retention of water
- The most important variable regulating antidiuretic hormone secretion is plasma osmolarity, or the concentration of solutes in blood. Osmolarity is sensed in the hypothalamus by neurons known as an osmoreceptors, and those neurons, in turn, stimulate secretion from the neurons that produce antidiuretic hormone.
- (1) Action
  - ✓ V2-----Increase water permeability-----Use cAMP mechanism--two kidneys so V2
  - ✓ V1------Cause vasoconstriction------Use IP3/Ca<sup>2+</sup> mechanism
- Factors stimulating ADH/Increase ADH:
  - √ Increase plasma Osmolarity
  - ✓ Decrease blood volume (hypovolemia, decrease ECF volume) and decrease BP
  - ✓ Pain, emotion, stress, exercise, standing, hypoxia and Nausea
  - ✓ Angiotensin II, Drugs—NMC----Nicotine, Morphine, Cyclophosphamide
- Factors inhibiting release/Decrease ADH:
  - / Decrease plasma Osmolarity
  - ✓ Increase blood volume and increase BP
  - ✓ Drugs-----Clonidine, Haloperidol and Alcohol



#### Aldosterone

- It is steroid hormones synthesized in the zone glomerulosa and act by gene activation It is potent and chief mineralocorticoid (half-life of mineralocorticoid is 20min)
- In the plasma, 40% Aldosterone circulate in free form and 60% in bound form
- It is usually called lifesaving hormones because, its absence causes death within 3 days to 2 weeks
- Physiological role:
  - The greatest effect on cortical collecting duct
  - The major function of Aldosterone is vasoconstriction
  - Regulates both the Reabsorption of Na<sup>+</sup> and excretion of K<sup>+</sup>
  - Secretion of H<sup>+</sup> into renal tubules
  - It maintains the Osmolarity and volume of ECF
  - Aldosterone is inhibited by an increase in serum Osmolarity
- Who regulates Aldosterone secretion? Regulated by
  - Angiotensin II
  - Hyperkalemia: serum potassium concentrations are the most potent stimulator of aldosterone secretion
- Removal of adrenal cortex result in:
  - Na<sup>+</sup> and water loss, but Na<sup>+</sup> loss excess then water
  - Result in decreased in ECF volume, produce hypotension, dehydration, circulatory collapse, finally death
  - Retention of K\* Produce hyperkalemia, dehydration and circulatory collapse
  - THEREFORE ALDOSTERONE IS ESSENTIAL FOR LIFE

### Angiotensin II

- · Renin catalyzes the conversion of angiotensinogen to angiotensin I in plasma
- . The Angiotensin-converting enzyme catalyzes the conversion of Angiotensin I to angiotensin II in lung capillary endothelium
- Renin is an enzyme, angiotensin I is inactive and Angiotensin II is physiologically active
- Angiotensin II is degraded by angiotensinase. One of the peptide fragments, angiotensin III, hair some of the biological activity of the angiotensin II
- Angiotensin II has four effects:
  - ✓ It stimulates the synthesis and secretion of Aldosterone by the adrenal cortex.
    - The Aldosterone increases Na reabsorption by the renal distal tubules, thereby increasing ECF volume, blood volume and arterial pressure
    - This action of Aldosterone is very slow because it requires new protein synthesis
    - Angiotensin II exerts its effect by the activity of Aldosterone
  - ✓ It increases Na\*-H\* exchange in the PCT:
    - This action of angiotensin II leads to contraction alkalosis
  - ✓ It increases thirst and therefore water intake.
  - ✓ It causes vasoconstriction of the arterioles, thereby increasing TPR and arterial pressure Major, short and transient action of angiotensin II is vasoconstriction
- Renin: Secreted by Juxtaglomerular cells
  - Factors stimulating renin secretion: Low BP, Hyponatremia, sympathetic stimulation catecholamines and erect postures
  - ✓ Factors inhibiting renin secretion: drugs like beta-blockers and NSAID

### Chapter 12

Renal Physiology and Pathology

### Atrial Natriuretic Peptide (ANP)

- ANP is released from atrial myocytes in response to increasing volume and atrial pressure.
- It Cause generalized vascular relaxation and decreases sodium (Na\*) reabsorption at the medullary collecting tubule.
- It constricts efferent renal arterioles and dilates afferent arterioles (cGMP mediated)
- Promoting diuresis and contributing to the "escape from Aldosterone" mechanism

### Naseem Sherzad High-Yield Points

- Sodium absorption------Aldosterone
- Sodium excretion-----ANP
- Net sodium absorption -----------------------Aldosterone and ANP
- Mole for mole sodium absorption------Aldosterone
- ADH is inhibited by------Alcohol
- Powerful stimulus for ADH is -----Nausea
- Powerful stimulus for renin is ------Sympathetic stimulation
- Powerful stimulant for Aldosterone------K\*
- · Powerful stimulant for angiotensin II is-----Na'
- \* The Most common cause of potassium shift from ICF to ECF is vigorous exercise

### Some Important Reflexes

### Oculocardiac reflex

- Stretch receptor present on eye Extraocular muscles----afferent through the short and long ciliary nerve of the ophthalmic branch of the trigeminal nerve -----efferent Via vagal fibers-----
  - ---increase parasympathetic vagus nerve------ causing bradycardia

## Hering-Breuer reflex

- Pulmonary stretch receptor also called slowly adapting pulmonary stretch receptors in bronchia and bronchioles, responsible for Hering-Breuer reflex
- Transmit signals through the Vagi into the dorsal respiratory group of neuron when the lung becomes overstretched
- Hering-Breuer reflex Check overinflation of lungs

### Baroreceptor reflex

- Include a fast neural mechanism
- Negativé feedback mechanism

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- Responsible from minute-to-minute regulation of BP
- Baroreceptors are more sensitive to change in arterial pressure
- Produce the greatest response to Rapidly decreasing arterial pressure
- Baroreceptors mechanism oppose any increase or decrease in arterial pressure, therefore, it is

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Renal Physiology and Pathology

called pressure buffer mechanism

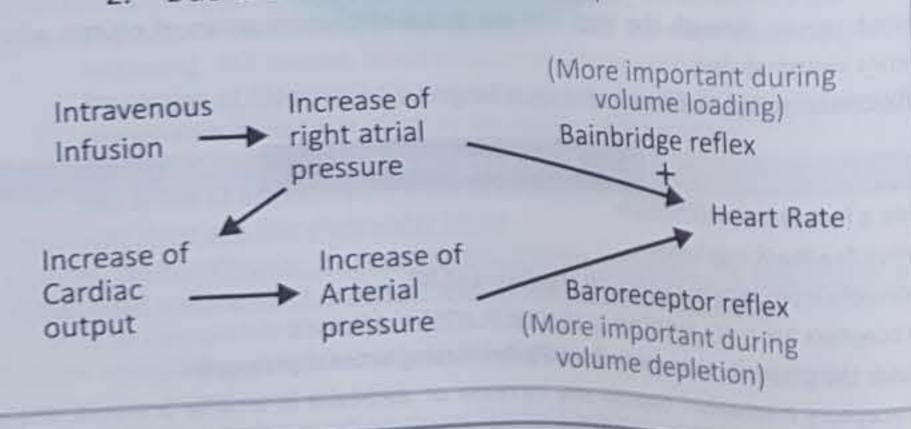
- Baroreceptors are stretch receptors found in the wall of the carotid body, aortic body and wall of all large arteries of the neck and thorax
- Location and innervation:
- ✓ In the wall of the Carotid sinus → Hering's nerve → a branch of Glossopharyngeal nerve to →Tractus solitarius in the medulla
  - ✓ In the wall of the aortic arch → the vagus nerve (cranial nerve X) → traveling to the Nucleus Tractus solitarius in the medulia
- Mechanism:
  - → decreasing the firing of the carotid sinus nerve→ which carries information to the vasomotor center in brain →response of vasomotor center →to decrease in mean blood arterial pressure -> by decreased parasympathetic(vagal) outflow to the heart and increase sympathetic outflow to heart and blood vessels

### Bainbridge reflex-also called atrial reflex

- When arterial pressure increase-→due to increase in blood volume----→SA node stretched-----> stretch receptors of the atria stretched and stimulated and send afferent signals via the vagus
- Bainbridge reflex can be blocked by atropine, is diminished or absent when the initial heart rate is high, and can be abolished by cutting the vagus nerves.

### Bainbridge Reflex

- Acceleration on of heart rate by increased right atrial pressure
- 2. Due to stimulation of atrial receptors



## Step Wise Approach to Acid-Base Disturbances

### Normal value:

- \* pH-----7.35-7.45
- \* PCO2-----35-45
- \* HCO3-----23-29

The arterial blood gas is used to evaluate both acid-base balance and oxygenation, each Representing separate conditions. Acid-base evaluation requires a focus on three of the reported components: pH, PaCO2 and HCO3. This process involves two basic steps.

### 1) Determine whether an Acidemia or an Alkalemia is present

- pH < 7.35 = Acidemia</p>
- pH > 7.45 = Alkalemia

### 2) What is the main disorder?

- Primary Metabolic (kidneys)
- Primary Respiratory(lungs)
- PCO2 = Respiratory component (lungs)
- HCO3 = Metabolic component (kidneys)
- It is determined by focusing at pCO2 (35-45)
- PCO2>45 = Respiratory Acidosis (if the pH is acidic)
- PCO2<35 = Respiratory Alkalosis
- if the pCO2 is normal then focus on HCO3 (23 29)
- HCO3 < 23 = Metabolic Acidosis
- HCO3 > 29 = Metabolic Alkalosis

## 3) For the FCPS part-1 acid base disorder questions they frequently ask for

- What is primary disorder?
- Is primary disorder compensated? If yes, fully compensated or partially compensated?
- Partially compensated = compensation started but pH is still abnormal.
- Fully compensated =compensation has normalized the ph.
- So pH tells you the answer.
- A few times a scenario of mixed disorder given.

### 4) Clues to 'Mixed' Disorder

- PaCO<sub>2</sub> and HCO<sub>3</sub> move in opposite directions
- Normal pH with abnormal PaCO<sub>2</sub> and HCO<sub>3</sub>
- pH changes in the opposite direction of a known primary disorder.

### 5) Summary:

- pH.....acidosis / alkalosis.
- pCO2, if normal then HCO3,.....primary disorder.
- Compensation.....in direction of primary disorder/change.
- pH.....to know compensation is fully or partially.

### Chapter 12

Renal Physiology and Pathology

- The Bulk of acid in the body is due to----anaerobic respiration
- Acute cases: For every 1 mmHg rise in CO<sub>2</sub>, HCO<sub>3</sub> rise 0.1meq/l
- Chronic cases: For every 1 mmHg rise in CO<sub>2</sub>, HCO<sub>3</sub> rise 0.4meq/l The Chemical acid-base buffer system is the first-line defense in the acid-base
- disturbance and respiratory regulation is the 2<sup>nd</sup> line of defense in acid base disturbance
- ( ) Compensation:
  - Response to a primary metabolic acidosis: it consists of body
    - ✓ Buffer system,
    - ✓ Compensatory metabolic alkalosis,
    - ✓ Renal acid excretion:
      - Aminogenesis—in fact three bicarbonate molecule are generated for each ammonia produced in the renal tubules from glutamate
      - H-ATPase activity

### The Specific Gravity of Urine

- Specific gravity is a measure of the density (weight) of the dissolved particle in the urine OR¢ measure of how concentrated urine is
- Normal range: 1.003 to 1.035
- Measured by urinometer and refractometer
- Assess the kidney ability to selective reabsorb water and essential mineral
- Asthenuria or isosthenuria is the complete loss of concentrating and diluting ability, due to there being no concentration gradient at all. The specific gravity of the urine will be the same as the specific gravity of the filtrate (so no dilution or concentration has occurred). It occurs in the endstage of kidney failure and central diabetes insipidus (ADH deficiency)

### Acidosis cause Hypercalcemia and Alkalosis cause Hypocalcemia

#### Explanation

- Albumin: it is negatively charged and that will bind positively charged Ca<sup>++</sup>.
- Acidosis: Acidosis means the excess of H\* ions, that H\* will displace the Ca\* and will bind by itself to albumin, and that displaced Ca\* will cause increases free Ca+ and Hypercalcemia. Decrease protein binding, increase ionized Ca\*\*.
- Alkalosis: Alkalosis will cause more Cat to be bound to albumin, therefore total Cat may be normal but free (ionized) calcium is low (Hypocalcemia) and this will Leads to tetany, which is the earliest sign of hypocalcemia

### Dialysis

- Dialysis is required for Salicylates poisoning (when Alkalinization is not feasible or very high Salicylates level i.e. >4.4 mmol/L)
- Amount of glucose is more in dialyzing fluid (125) as compared to plasma(100)
- Amount of glocosconate(HCO3) is more in dialyzing fluid (35.7) as compared to plasma(24)
- The dialyzing fluid is identical to plasma but having no urea, urate, creatinine, sulfate, phosphale or any other excretory products

### Chapter 12

Renal Physiology and Pathology

## Acidosis and Alkalosis Examples

### (5) Anion gap:

- The Normal anion gap is 11
- . The "anion gap" (which is only a diagnostic concept) is the difference between unmeasured anions and unmeasured cation and is estimated as

Plasma anion gap = [Na\*] - [HCO3\*] - [Cl\*] = 144 - 24-108 = 12mEq/l

### 1) Metabolic acidosis with Normal anion gap

- Diarrhea
- Renal tubular acidosis
- Carbonic anhydrase inhibitors (Acetazolamide)
- Addison disease
- Pancreatic fistula

### 2) Metabolic acidosis with an increase in anion gap

- Lactic acidosis
- Ketoacidosis and Renal failure
- Progressive stage of shock

### 3) Metabolic alkalosis

- Excessive Vomiting (loss of stomach acid)
- Hyperaldosteronism
- Diuretic use
- Heavy ingestion of Antacid use
- Severe dehydration
- Endocrine disorder

### 4) Respiratory alkalosis

- Hyperventilation
- Aspirin ingestion(early)

### 5) Respiratory acidosis—hypoventilation

- Emphysema
- Acute lung disease
- Chronic lung disease
- Opioids, narcotics, sedative
- The Weakening of respiratory muscle

### 6) Effect of acidosis or alkalosis on body

- Acidosis------CNS depression------Coma
- Alkalosis------CNS over-excitability-----tetany
- 7) Hypokalemia and Hyponatremia are well-known complications in severe hyperemesis gravidarum, which may lead to metabolic alkalosis. Urine test for specific gravity and ketone is done daily till negative for at least for 2 days. Page | 351

Renal Physiology and Pathology

....

## Water Input and Output

## Water loss from the body per day:

- Lungs———350ml
- Skin-----350ml
- Feces------100ml
- Urine-----1400ml
- Sweats-----100ml
- The water loss through the skin and respiratory tract is called "insensible" water loss which is 700ml/day.

### 1 Intake:

- Fluids ingested:——2100ml
- From metabolism:—200ml
- Total intake:———2300ml

#### Output:

- Insensible-skin:----350ml
- Insensible-lungs:----350ml
- Sweat:-----100ml
- Feces:-----100ml
- Urine:----1400ml
- Total output:——2300ml

#### **Thirst**

#### (1) Thirst center:

- An area called the thirst center is located in the lateral hypothalamus
- ADH: release is coordinated with activity of the thirst center -regulate intake

### (3) Stimuli for thirst

- Increase ECF Na+
- Decrease ICF K+
- Angiotensin II
- Hemorrhage---fluid loss Decrease cardiac output
- Dry mouth

### **Control of Thirst**

Increase thirst by	
✓ Increase Osmolarity ✓ Increase angiotensin II ✓ Decrease in blood volume ✓ Decrease in blood pressure ✓ Dryness of mouth	

# **PATHOLOGY**

Chapter 12

## Clinical Pearls

#### **Important Point for Diagnosis**

S/No.	Disease	Finding
Acute Pyelonephritis     WBC cast in urine		WBC cast in urine
2.	Acute cystitis	WBC's in urine
3.	Glomerulonephritis	RBC cast in urine
4.	Bladder carcinoma	RBC's in urine
5.	Chronic End-stage renal disease	Waxy casts
6.	Post-streptococcal glomerulonephritis	Cola or tea-colored urine

### Disease with Important Finding

S/No.	Disease	Finding
1.	IgA Nephropathy	Mesangial electron-dense deposit
2.	Type-1 MPGN, SLE nephritis	sub-endothelial deposit
3.	Type-2 MPGN	Intra membranous deposit
4.	Good pasture syndrome	Anti-GBM antibody
5.	Poststreptoccol GN	Sub-epithelial humps
6.	Membranous glomerulopathy	Sub-epithelial deposit
7.	Minimal change disease	Effacement of foot process of podocytes
8.	Good Pasture Syndrome	Hemoptysis + Hematuria
9.	Alport Syndrome	Deafness + Hematuria
10.	Wagener's Granulomatosis	Sinusitis + Hemoptysis + Hematuria

### Naseem Sherzad High-Yield Points

- IgA nephropathy, which is also known as Berger's disease, is the most common cause of the nephritic syndrome.
- \* Focal segmental glomerulosclerosis is the most common cause of nephrotic syndrome in adults.
- Minimal change disease is the most common cause of nephrotic syndrome in children.

Renal Physiology and Pathology

Renal Physiology and Pathology

# HIGH YIELD POINTS

- IgA nephropathy, which is also known as Berger's disease, is the most common cause of the
- Thromboangiitis obliterans, which is also known as Buergers disease, is strongly associated with smoking.
- IgA nephropathy is present with recurrent episodes of Hematuria.
- Poststreptoccol glomerulonephritis occurs 1-2 weeks after infection and C3 levels is low, while IgA nephropathy occurs 1-2 days after infection and C3 level is normal.
- 5) Membranoproliferative Glomerulonephritis (MPGN) may be nephrotic, nephritic or mixed. Light microscopy show Tram track appearance
- Type-1 MPGN results from activation of both classic and alternative complement pathways. It is the most common type.
- 7) Type-2 MPGN, which is also known as "dense deposit disease" or "alternative MPGN" which result from activation of the only alternative pathway. It is associated with the C3 nephritic factor. There is a very low C3 level.
- 8) The characteristic histological finding associated with RPGN is the presence of crescents (Crescentric GN). These distinctive lesions of proliferation are called crescents due to their shape as they fill Bowman's space. Crescents are formed both by the proliferation of parietal cells and by the migration of monocytes/macrophages into Bowman's space
- 9) Membranous Glomerulopathy= electron microscopy show= spike and Dome appearance of membrane on silver stains. Sometimes cause renal vein thrombosis.
- 10) In post-streptococcal GN, tissue injury is causes by Complement activation.
- 11) Focal segmental glomerulosclerosis is the most common cause of nephrotic syndrome in adults Causes of focal segmental glomerulosclerosis are heroin addiction, HIV nephropathy, sickle cell disease, massive obesity & idiopathic.

### 12) Minimal change disease:

- Minimal change disease is also called "lipoid nephrosis" or "Nil disease" is the most common cause of nephrotic syndrome in children.
- . It may be associated with Hodgkin Lymphoma and the most characteristic feature is its usually dramatic response to corticosteroid therapy.
- 13) The primary bladder defense is voiding (from Campbell-Walsh urology)
- 14) Most recurrent infection in the female patient are reinfections
- 15) The most reliable urine specimen is obtained by suprapubic aspiration.
- 16) The validity of a midstream urine specimen should be questioned if microscopy reveals squamous epithelial cells
- 17) Rapid screening methods for detecting UTI s should be used primarily for low-risk asymptomalia patients.
- 18) The most accurate test for the evaluation of infection in the kidney is the urethral catheterization
- 19) The cure of UTI s depends most on an antimicrobial agent's urine level.

- 20) The drug of choice for uncomplicated cystitis in most young women is TMP-SMX.
- 21) The optimal duration of antimicrobial therapy for symptomatic acute uncomplicated cystitis in women is 3 days.
- 22) Screening for bacteriuria is beneficial in pregnant women.
- 23) Nitrofurantoin prophylaxis is effective because of the concentration of the drug in the urine.
- 24) The ideal antimicrobial agent for self-start therapy for a UTI is a fluoroquinolone.
- 25) The most common bacterial cause of xanthogranulomatous pyelonephritis is Proteus mirabilis
- 26) The most reliable early clinical indicator of septicemia is hyperventilation
- 27) Compared with non-pregnant women, pregnant women have a higher prevalence of acute pyelonephritis.
- 28) The drug thought to be safe in any phase of pregnancy is penicillin.
- 29) In spinal cord-injured patients the bladder drainage technique with the lowest complication rate is clean intermittent catheterization (CIC).
- 30) A distinctive and diagnostic feature of renal oncocytoma is the presence of multiple mitochondria on electron microscopy.

### 31) Wilms tumor/nephroblastoma:

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- ✓ It is the most common malignant renal tumor in children; the average age is 3 years, comprised of the blastema, primitive glomeruli, tubules and stromal cells.
- ✓ Wilms tumor metastases occur in the lung in 92% and liver 18 %
- ✓ Present as a large, unilateral flank mass with Hematuria and hypertension.

## Good pasture syndrome

- Only in Good pasture syndrome, there is linear IgG and C3 deposit along the basement membrane remaining all give the granular deposit.
- Good pasture syndrome= Type II hypersensitivity reaction caused by Anti- basement membrane antibodies against collagen type 4, in glomerular and pulmonary capillaries.

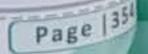
### Alport syndrome

- Electron microscopy shows "Basket and wave" appearance of GBM I-e area of GBM thinning alternating with the area of thickening
- Alport syndrome= Defective GBM synthesis due to abnormal collagen type 4

## Minimal Change Disease

### (3) Morphology:

- · Light microscopic: No change
- \* Electron microscope:
  - ✓ The principle lesion is in visceral epithelial cell
  - ✓ The visceral epithelial cell show diffuse effacement of foot process
  - ✓ The cell in proximal tubules are laden with lipid and protein (lipid nephrosis)
- Immune fluorescence microscopy: No change



Acute Post-Streptococcal Glomerulonephritis

### (2) Causative agent:

Group A streptococcus(streptococcus pyogenes)

### ( Morphology:

- Light microscopy:
  - Hypercellularity and enlarge glomeruli
  - ✓ Leukocytes infiltration, lumpy bumpy appearance
- Electron microscopy:
- ✓ <u>Subepithelial humps</u> which are formed by Ag-Ab complex at epithelial cell surface
- Fluorescence microscopy:
- ✓ Granular appearance due to IgG, IgM and C3 along GBM and mesangium

### How the conditions developed/pathogenesis:

- Occur 1-4 weeks after a sore throat caused by group A B-hemolytic streptococci i.e. streptococci pyogenes.
- It is developed by the glomerular deposition of the immune complex resulting in proliferation and damage to glomerular cells and infiltrate of leukocytes especially neutrophil,
- It is a Type III hypersensitivity reaction

### Other condition which can produce such a scenario:

- Hepatitis C and HIV
- Mumps
- Measles
- Infectious mononucleosis
- Malaria
- Chickenpox

### **Renal Stones**

- Types of renal stones: Calcium stone, Struvite stone, uric acid stone and Cystine stone
- Calcium oxalate (60%), is the most common type of kidney stones, 90% of stones contain calcium and are seen on X-ray. 2<sup>nd</sup> most common is phosphate.
- <u>Uric acid stones</u> are radiol<u>U</u>cent and non-visible on X-ray but visible on CT and Ultrasound, having a strong association with Hyperuricemia.
- Magnesium ammonium phosphate (MAP) which is also called "Struvite" or "Stag-horn calculi" of "infection stone" or "Triple phosphate" form the largest renal stone, which is caused by ureast positive organism like Proteus vulgaris.
- Cystine stone most often secondary to cystinuria and is hexagonal crystals.
- Radio-opaque are those which can be seen on X-ray while radiolucent (uric acid stone) are those which can't be seen on x-ray
- Clinical presentation of renal stone is colicky pain, Hematuria and unilateral flank tenderness fever is usually absent.
- Renal stone can lead to severe complication like Hydronephrosis and pyelonephritis
- Ileal disease or resection increase absorption and urinary excretion of Oxalate leading to kidner

- stone formation
- Least chance of renal stone is associated with hyperlipidemia
- Citrate inhibits stone formation by complexing calcium, thereby lowering urinary saturation of calcium oxalate. In addition it inhibits spontaneous precipitation of calcium oxalate and agglomeration of calcium oxalate crystals. It also inhibits calcium oxalate and calcium phosphate crystal growth, with its effect on calcium phosphate crystal growth more pronounced than on calcium oxalate crystal growth. Last, it prevents heterogeneous nucleation of calcium oxalate by monosodium urate
- The primary mechanism of action of citrate is as a complexing agent for calcium in urine, thereby reducing ionic calcium and urinary saturation of calcium oxalate.
- Intestinal oxalate absorption is modulated by dietary oxalate and calcium intake and by the presence or absence of O. formigenes. In the setting of a high calcium intake, oxalate absorption decreases, and during calcium restriction, oxalate absorption increases because of reduced formation of a soluble calcium oxalate complex and increased availability of oxalate for absorption.
- Acid-base status determines urinary citrate excretion. Metabolic acidosis reduces citrate excretion by augmenting citrate reabsorption and mitochondrial oxidation, whereas alkalosis enhances citrate excretion.
- Hypercalciuria is the most common abnormality identified in calcium stone formation. Hypercalciuria is defined as a urinary excretion greater than 4 mg/kg/day.
- Calcium absorption occurs primarily in the small intestine at a rate that is dependent on calcium intake.
- The most important determinate of uric acid stone formation is low urinary pH. Low urinary pH in uric acid stone formers is likely due to impaired ammoniagenesis associated with insulin resistance.
- Medications which may precipitate as stones include Triamterene, silica, indinavir, ephedrine, and ciprofloxacin.
- Intestinal hyperabsorption of oxalate in patients with enteric hyperoxaluria is the most significant risk factor leading to recurrent calculus formation.

Reference: Campbell's Walsh Urology 11th edition

### Acute renal failure

- Normal BUN: Creatinine ratio is 15, this ratio is an increase in pre-renal failure and post-renal failure, this ratio is decreased in intrinsic renal failure
- Acute tubular necrosis (ATN) is the most common cause of acute renal failure.
- Fever, Rash, eosinophilia and esospinophiluira are the classical feature of acute interstitial nephritis (drug-induced)

- The most common cause of chronic kidney disease is diabetes mellitus. Cardiovascular disease is the most common cause of death in chronic kidney disease.
- Infection is the second most common cause of death in chronic kidney disease. Anemia in CKD is due to loss of erythropoietin, there is low retics counts, bleeding in CKD is due to
- platelets, which are normal in number but they don't degranulate/ platelet dysfunction
- Hypocalcemia is due to loss of alpha-1 hydroxylase and there will be hyperphosphatemia because high PTH level releases phosphates from bones but kidneys are unable to excrete it. The parathyroid gland will be hypertrophied
- Patient with CKD will have metabolic acidosis
- Treatment of anemia in CKD patient: inj erythropoietin
- Absolute contraindicated antibiotic: Tetracycline
- Relative contraindicated: aminoglycosides (Gentamycin), cephalosporin, sulpha drugs Fluoroquinolones
- Relative safe: penicillin, vancomycin, Macrolide, Metronidazole

### Stages of CKD

Stage	Description	GFR
Jiage 1	Kidney damage with normal GFR or increase GFR	>90
2	Kidney damage with mild decrease in GFR	60-89
3	Moderate decrease GFR	30-59
4	Severe decrease GFR	15-29
5	Kidney failure	< 15 (dialysis)

### Rena Cell Carcinoma (RCC)

- Patient present with the classic triad of Hematuria, Flank pain and Palpable mass secondary Polycythemia also occurs in RCC
- Gene deletion occur on chromosome 3
- · Microscopically, clear cell carcinoma is the most common histological subtype with papillary. chromophobe and collecting duct tumor making up the remaining 15%.
- Rarely may presents with left-sided varicocele, can extend into right atria.

THE RESIDENCE	Neuroblastoma	Wilms tumor
Associated syndrome	with Opsoclonus-myoclonus	Associate with WAGR syndrome, beckwith wiedemann syndrome and hemihypertrophy
May cross the	midline	Usually does not cross the midline
May cross un	and immobile	Maybe displaced
Osually lixed	more common and Punctate	Calcification: less common (15%)
	the second of th	Retroperitonal
Retroperiton		common 13%)

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Renal Physiology and Pathology

### Polycystic Kidney Disease

- ADPKD is strongly associated with berry aneurysm of circle of Willis in the brain that can lead to subarachnoid hemorrhage.
- The most common cause of death/complication in ADPKD is renal failure.
- Medullary cystic disease modality of choice: Contrast enhanced CT-scan
- Multicystic disease: Most diagnosed on a prenatal ultrasound scan. Ref: Bailey & Love's Page 1399

ADPKD	ARPKD	
Most common	Most severe	
Autosomal dominant	Autosomal recessive	
Onset age > 30 year	Infant and children	
Half get ESRD by age 60	Infant renal failure	
Cerebral aneurysm	Liver fibrosis, death	

### The Genetics of ADPKD

PKD1	PKD2
Located on chromosome 16	Located on chromosome 4
Codes for polycystin-1 protein (PC1)	Codes for polycysein-1 protein (PC1)
Associated with more severe phenotype	Less severe phenotype
Incidence: 85%	Incidence: 15%

### Hematuria

- Hematuria, or Haematuria, is the presence of red blood cells in the urine.
- Renal stone is the most common upper urinary tract cause of Hematuria
- Infection is the most common cause of lower urinary tract Hematuria
- Transitional cell carcinoma of bladder is the most common non-infectious cause of lower urinary tract Hematuria-----Painless Hematuria (most constant & persistent features of Ca bladder )---

### Left side varicocele

- It occurs as left testicular vein opens into the renal vein which may be blocked by tumor leading to left-sided varicocele.
- Occur most commonly in renal cell carcinoma.

## Acute renal failure (acute kidney injury)

There are three-sub types:

### A. Pre-Renal Failure:

- It is the most common cause of acute renal failure 70% and potentially reversible
- Lab diagnoses show hyaline caste

### B. Intrinsic Renal Failure: Caused by:

### i. Acute Tubular Necrosis (ATN)

- It is the most common cause of intrinsic renal failure
- Which may be cause by ischemia (Ischemic ATI) or toxin (Toxic ATI)
- Most common drugs Aminoglycosides, Methotrexate And Cisplatin

VASED IN SHIER WATER EVEN ALL HAVE

- Lab show granular "muddy brown" cast
- ✓ Initial phase: it lasts for about 36 hours, the slight decline in urine output with a rise in Clinical course:
  - ✓ Maintenance phase: Oliguria with raised BUN, <u>hyperkalemia</u> with metabolic acidosis
  - ✓ Recovery phase: rise in urine volume, hypokalemia and increased in vulnerability to infection

### ii. Acute Interstitial Nephritis (AIN)

Caused by:

- Drug (drug-induced acute interstitial nephritis)
- Most common drugs Penicillin, cephalosporin, Rifampin, Allopurinol, furosemide and thiazide diuretic
- Pyelonephritis
- Lab show: RBCs, WBC,s caste and eosinophils

### iii. Glomerulonephritis

### C. Post Renal Failure

- It is the least common type of acute kidney injury.
- It is caused by obstruction.

### Difference between Nephritic and Nephrotic syndrome

### 1) Nephrotic syndrome:

Definition: Glomerular disease Characterized by: Mnemonic: HMG

- Hypoalbuminemia, hyperlipidemia and lipiduria
- Massive proteinuria
- Generalized edema (due to Hypoalbuminemia)

#### Causes:

- A. Primary glomerular disease: FM3
  - ✓ Focal segmental glomerulosclerosis
  - ✓ Minimal change disease
  - ✓ Membranous glomerulopathy
  - ✓ Membranoproliferative glomerulonephritis
- B. Systemic disease
  - ✓ Diabetes mellitus
  - √ SLE
  - √ Amyloidosis
- 2) Nephritic syndrome: Mnemonic HOPE Hematuria and hypertension

  - Oliguria
  - Proteinuria (<3.5gm/day)</li>
  - Edema (due to salt retention)

#### Causes:

- ✓ Post-streptococcal glomerulonephritis
- ✓ IgA nephropathy
- ✓ Rapidly progressive glomerulonephritis

### Chapter 12

### Renal Physiology and Pathology

### 1) Benign:

- a) Renal oncocytoma
- b) Renal papillary adenoma
- Renal Fibroma (Hemartoma)
- d) Angiomyolipoma

### 2) Malignant:

- I. Renal cell carcinoma: Subtypes
  - a) Clear cell carcinoma (70-80 %)

#### Gross feature:

- ✓ It is typically a solitary tumor, with multifocality
- ✓ Commonly present as a well-circumscribed mass with capsule or pseudo-capsule and a pushing margin.
- ✓ On cut section, CCRCC is typically a golden color because of the accumulation of lipid in the malignant cells, while areas of hemorrhage (brown), fibrosis (gray), necrosis, and cystic degeneration often give a variegated appearance.

#### Microscopic features:

- √ Clear cytoplasm
- ✓ Delicate branching vasculature often called "chicken-wire-like" vasculature-----Key feature
- ✓ Polygonal cell with the central nucleus
- b) Papillary carcinoma (10-15 %)
- Chromophobe renal cell carcinoma (5 %)
- d) Collecting duct carcinoma (1 %)

### **Renal Function Test**

### (3) Urinalysis

- Physical examination
- Chemical examination
- Microscopic examination

### Test for glomerular function:

- Creatinine clearance
- Urea clearance Inulin clearance

### Blood urea nitrogen:

- Normal BUN range is 8-25 mg/dl
- BUN is the most sensitive indicator of renal disease
- Increased BUN is = Azotemia

### (3) Creatinine

- The Breakdown product of creatine phosphate released from skeletal muscle at a steady rate.
- It is the gold standard investigation for renal function.
- It is filtered by the glomerulus
- Normal range is 0.6-1.3 gm/dl
- Creatinine clearance in mild renal failure is 60-80%

# PELVIS AND PERINEUM



#### Uterus

### Support of Uterus

- . The uterus is supported mainly by the tone of the levator Ani muscle and the condensation of the pelvic fascia, which form three important ligament
- ❖ Passive support: Cardinal ligament and Sacro-cervical ligament
- . Active/dynamic support: Pelvic diaphragm made of levator ani muscle
  - 1) Cardinal ligament or Mackenrodt's ligament or transverse cervical ligament
    - It is the condensation of pelvic fascia that pass to the cervix and upper end of the vagina from the lateral wall of the pelvis
    - This ligament provided Major/main support to the uterus
    - Prevent uterus from Prolapse
    - Strongest ligament
    - Uterus remain in position by this ligament
    - Injured during uterovaginal Prolapse
  - 2) Sacro-cervical ligament
  - 3) Pubo-cervical ligament
- M Normal anatomical position:
  - Anteverted
  - Anteflexed

### Three Anteroposterior Diameter

- True conjugate: The anatomical of true conjugate is measured from the promotory of the sacrum to the centre of the upper surface of the Symphysis pubis and measures approximately 12 cm although it is slightly longer than the obstetric conjugate, the extra space is not available for the passage of the fetus
- Obstetric conjugate: This diameter extends from the sacral promontory to the upper inner border of the Symphysis pubis and measures approximately 11 cm. this is the first boney strait through which the fetus has to pass
- Diagonal conjugate: The diagonal conjugate is measured anterio-posteriorly from the apex of the pubic arch of Symphysis to sacral promontory

### Chapter 13

### **Pelvis and Perineum**

#### **Blood supply**

- . Arteries: The arterial supply to the uterus is mainly from the uterine artery, a branch of the internal iliac artery
- . Veins: The uterine vein follows the artery and drains into the internal iliac vein

#### Lymphatic drainage

- . The lymph vessels from the fundus of the uterus accompany the ovarian artery and drain into the para-aortic nodes at the level of the first lumbar vertebra
- . The vessels from the body and cervix drain into the internal and external iliac lymph node
- . A few lymph vessels follow the round ligament of the uterus through the inguinal canal and drain into the superficial inguinal lymph nodes

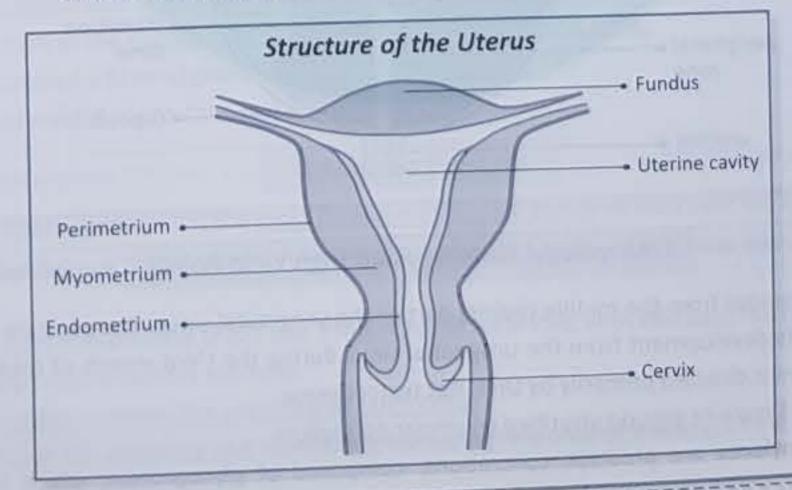
### The wall of uterus consists of three layers

- Perimetrium:----it is thin outer layer
- b) Myometrium:----it is thick smooth muscle layer
- Endometrium:-----it is the innermost layer and can be distinguished into:
  - Basal layer

- Deepest tissue of endometrium, adjacent to myometrium
- This layer regenerates after each cycle
- It contains the blind end of gland. It has its own blood supply and is not sloughed off during menstruation

#### Functional layer

- This provide a proper site for implantation
- This layer shed or lost during menstruation because of ischemic necrosis due to withdrawal of estrogen and progesterone
- It consists of compact and spongy layer and shed at menstruation and parturition
  - ✓ Compact layer: it is the thin and superficial layer and consist of densely packed stromal cells
  - ✓ Spongy layer: it is thick and composed of edematous stroma which contains dilated tortuous bodies of uterine gland



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NAME AND POST OFFICE ADDRESS OF THE OWNER, WHEN PERSON NAMED IN COLUMN 2 IS NOT THE OWNER, THE OWNE

**Pelvis and Perineum** 

Prostate

# ₩ Zonal/McNeal Classification: often used in Pathology

- Peripheral zone:—<u>largest zone</u> and touch the rectum, contain 70-75% of normal prostate glandular tissue. Most common site for Prostate Adenocarcinoma
- Central Zone:
- Transitional zone: Common site for BPH

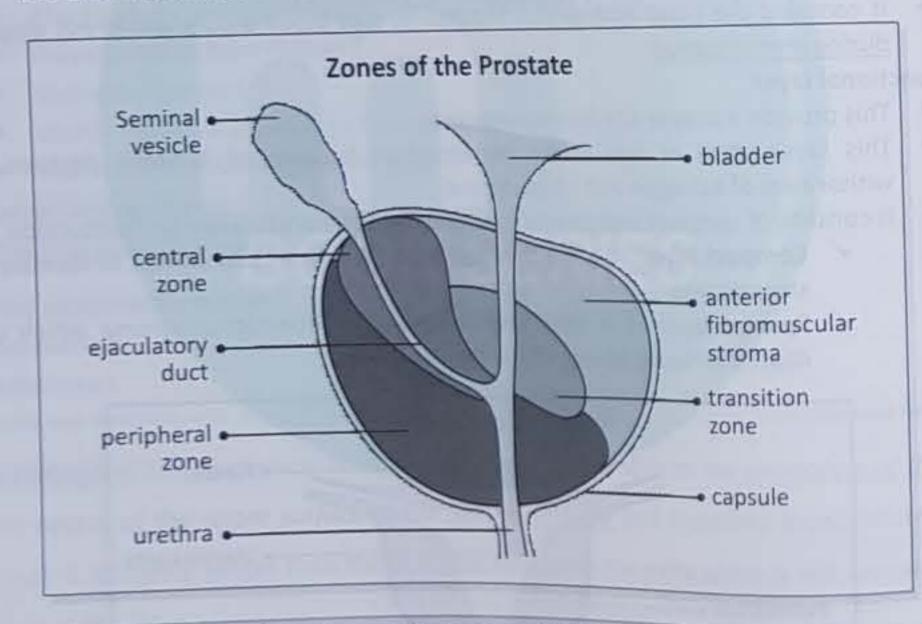
## W Lobular Classification: More often used in anatomy

- Anterior lobe (or isthmus): lies in front of the urethra and devoid of glandular tissue roughly corresponds to part of transitional zone
- Posterior lobe---correspond to Peripheral zone, can be palpated through the rectal wall
- Median or middle lobe-correspond to the central zone
- Left and right Lateral lobe——Largest lobe, Span all zones

#### M Clinical Points:

AND RES OF REAL PROPERTY.

- The arteries seen at 5 and 7 o'clock after middle lobe resection of the prostate during TUR are urethral branches of the inferior vesical arteries known as Badenoch's arteries.
- The small arteries seen at 2 and 10 o'clock are known as Floch's arteries



### Embryology, Histology and High Yield Points

- Prostate develops from the middle (pelvic) part of the urogenital sinus. The prostate first appeals and starts its development from the urogenital sinus during the third month of fetal growth and development is directed primarily by DHT, not testosterone.
- Epithelium: Simple or pseudo-stratified columnar epithelium
- Corpora amylacea are prostatic concretions, composed of glycoprotein, which may become

calcified, their number increases with age

- Transitional zone arises from mesoderm, peripheral zone arises from endoderm and central zone appears to be Embryologically distinct possibly müllerian origin
- The prostate contains a rich plexus of autonomic nerves.
- The source of citrate, zinc, spermine, and choline is the prostate.
- prostatic fluid is more acidic than is serum.
- The most common of the two 5α-reductase isoforms in the benignly enlarged prostate gland is type 2.
- BPH is characterized by an increased number of epithelial and stromal cells, not an increase in their size.
- Prostatic stroma represents 40% of the gland. Smooth muscle is a prominent component of the stroma.
- Androgen withdrawal results in apoptosis of prostate cells
- Estrogen receptors are found in the prostate and may play a role in BPH.
- Prostate smooth muscle tension has been shown to be mediated by the α1<sub>a</sub> adrenergic receptors.

### Denonvilliers fascia

- The rectoprostatic fascia (Denonvilliers' fascia) is a membranous partition at the lowest part of the rectovesical pouch.
- It separates the prostate and urinary bladder from the rectum.
- This layer should be preserved on the safe side during Prostatectomy to prevent the development of a rectourethral fistula.

### Benign prostate hyperplasia (BPH)

- It arises from submucosal gland in the transitional zone.
- Histologically BPH is <u>fibromyoadenoma</u>.

- Dihydrotestosterone is strongly involved in the development of BPH
- The formation of the middle lobe in BPH arises from the central zone.
- It not considered a premalignant lesion.
- The Normal weight of prostate----18-20g

### Carcinoma Prostate

- Name and Address of the Owner, when the Party of the Owner, when the Owner, which the Owner Prostatic Adenocarcinoma is the most common malignant tumor of men over the age of 65 years.
- It originates from prostate gland proper in the peripheral zone or posterior lobe of the prostate
- Prostatic acid Phosphatase (PAP) and PSA (increase total PSA, with decrease fraction of free PSA) are the most useful tumors markers.
- Prostate biopsy confirms the presence of carcinoma.
- PSA uses both for screening and monitoring (assessing response of therapy) of the prostate.

### Chapter 13

### Bone Metastasis

- Metastasis to the bone is common in Breast> prostate> lung cancers.
- The Vertebral column is the most common site
- Batson paravertebral venous plexus is responsible for the predilection of bone metastasis to the site

### M Osteoblastic tumor:

- ✓ Prostate cancer is the most common cancer-producing osteoblastic (bone-forming) metastasis, second most common is breast cancer
- ✓ That's why, there is no Hypercalcemia in prostate cancer but predispose to hypocalcemia. and secondary hyperparathyroidism
- ✓ Serum alkaline Phosphatase (ALP) is elevated because osteoblast use this enzyme in bone formation

### Osteolytic tumor:

- ✓ Cancer that commonly produce Lytic metastasis include lung cancer, renal carcinoma and breast carcinoma
- ✓ Hypercalcemia is possible if Osteolytic lesion is extensive.
- Bone pain from metastasis is treated with localized radiation

### Penis, Scrotum and Vagina

#### Penis

- . Lymphatic drainage: The skin of the penis is drained into the medial group of superficial inguinal nodes. The deep structures of the penis are drained into the internal iliac nodes
- . Nerve supply: The nerve supply is from the pudendal nerve and the pelvic plexuses.
- . Corpora cavernosa: The Paired mass of erectile tissue that contain irregular vascular space lines by a continuous layer of endothelial cells
- . Corpora spongiosum: Single mass of erectile tissue that contains vascular space of uniform size NAME AND POST OFFICE ADDRESS OF

#### Scrotum

### M Nerve supply:

-----

- . The anterior surface of the scrotum is Primarily supplied by the ilioinguinal nerves and the genital branch of the Genitofemoral nerves provides a smaller contribution
- The posterior surface is supplied by branches of the perineal nerves and the posterio cutaneous nerves of the thigh.

### M Blood supply:

- . The external pudendal branches of the femoral and scrotal branches of the internal pudendal arteries supply the scrotum.
- The veins accompany the corresponding arteries.

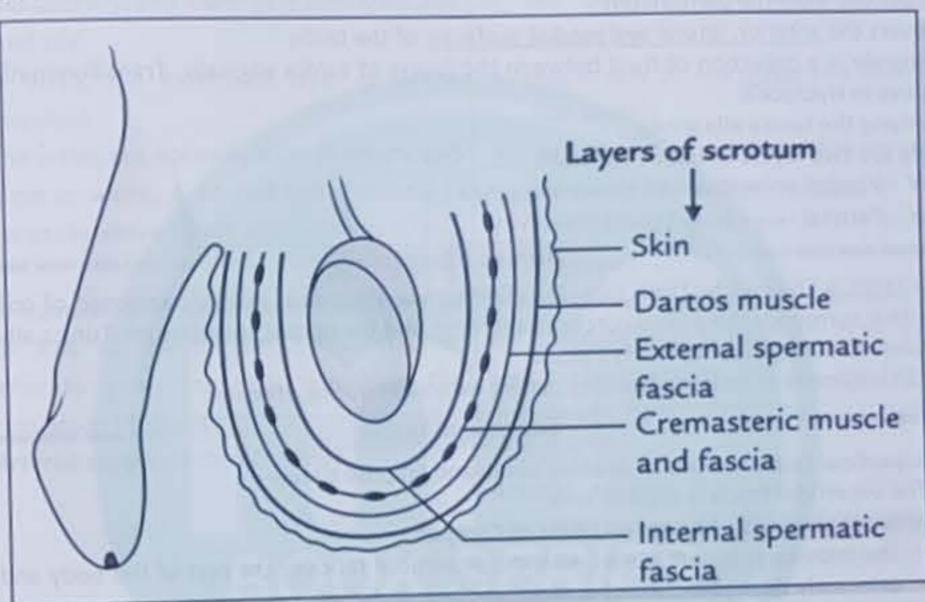
### M Lymph drainage:

- . The wall of the scrotum is drained into the medial group of superficial inquinal lymph node
- The wall of the scrotum has the following layers: Some Damn Englishman Called It The Testes

Chapter 13

#### **Pelvis and Perineum**

- . Superficial fascia; the Dartos muscle, which is smooth muscle, replaces the fatty layer of the anterior abdominal wall, and Scarpa's fascia (membranous layer) is now called Colles' fascia.
- . External spermatic fascia derived from the external oblique
- . Cremasteric fascia derived from the internal oblique
- Internal spermatic fascia derived from the fascia transversalis
- Tunica vaginalis, which is a closed sac that covers the anterior, medial, and lateral surfaces of each testis
- \* Testis



#### Vagina

- The vaginal lining has no glands; therefore, the vagina is lubricated by secretion from the cervical
- \* The mucosa is composed of a thick, stratified squamous non-keratinized epithelium and fibroelastic connective tissue, the lamina propria that is highly vascular.
- Vaginal epithelial cells have a relatively high concentration of glycogen compared to other epithelial cells of the human body. The metabolism of this complex sugar by the lactobacillus dominated microbiome to produce lactic acid, which is responsible for vaginal acidity.
- Blood supply: The arteries supplying the superior part of the vagina derive from the uterine arteries. The arteries supplying the middle and inferior parts of the vagina derive from the vaginal and internal pudendal arteries
- Hymen epithelium: stratified squamous epithelium
- \* Relations:

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- ✓ Lateral to upper part; ureter
- Lateral to middle part: the anterior fiber of levator ani
- ✓ Lateral to lower part: urogenital diagram

## **Processus Vaginalis**

- The vaginal process (or Processus vaginalis) is an embryonic developmental outpouching of the
- It is present from around the 12th week of gestation, and commences as a peritones. outpouchings.
- Cover testes only

### Tunica Vaginalis

It is derived from the peritoneum

THE RESERVE THE PERSON NAMED IN

- It covers the anterior, lateral and medial surfaces of the testis
- Hydrocele is a collection of fluid between the layers of tunica vaginalis, Transillumination test is positive in Hydrocele
- Overlying the tunica albuginea
- There are two layers of tunica vaginalis
  - ✓ Visceral
    ——Overlies tunica albuginea
  - ✓ Parietal ——Lines the scrotal cavity

### Tunica albuginea

- NAME AND ADDRESS OF THE OWNER, WHEN PERSON NAMED IN Each testis is covered by thick capsule called tunica albuginea, mainly composed of collagenous fiber that surrounds the paired corpora cavernosa and the corpus spongiosum. Tunica albuginea is not pierced during tapping for Hydrocele
- The arrangement of collagen bundles permit extension during erection

### Superficial fascia

- > Superficial fascia is made of Areolar tissue and adipose tissue
  - The superficial fascia is divided into:

### Superficial Fatty layer: Also called fascia of Camper

- The fatty layer is continuous with the superficial fat over the rest of the body and may be extremely thick (3 in. [8 cm] or more in obese patients)
- In the scrotum, the fatty layer of the superficial fascia is represented as a thin layer smooth muscle, the Dartos muscle.

## Deep Membranous layer: Also called Scarpa's fascia

- . The membranous layer is thin and fades out laterally and above, where it become continuous with the superficial fascia of the back and the thorax, respectively.
- Inferiorly, the membranous layer passes onto the front of the thigh, where it fuses with the deep fascia one fingerbreadth below the inguinal ligament.
- . In the midline inferiorly, the membranous layer of fascia is not attached to the pubis but forms a tubular sheath for the penis (or clitoris).
- . Below in the perineum, it enters the wall of the scrotum (or labia majora). From there passes to be attached on each side to the margins of the pubic arch; it is here referred to Colles' fascia.
- · Posteriorly, it fuses with the perineal body and the posterior margin of the perineal membrane

#### Deep fascia

PERSONAL PROPERTY AND PERSONS NAMED IN COLUMN 2 IN COL The deep fascia in the anterior abdominal wall is merely a thin layer of connective tissue coveri The deep fascia in the distribution of the membranous layer of superficial fascia.

Chapter 13

**Pelvis and Perineum** 

### Testes and ovary

#### Testes

### Position in the scrotum: The testis is Location: The ovaries are located in the suspended in the scrotum by the spermatic ovarian fossa on the lateral pelvic wall cord. It is located obliquely, so that its below the pelvic brim in nulliparous adult upper pole is leaned somewhat forwards women. A negligible peritoneal depression and laterally, and lower pole backward and is the ovarian fossa which is also medially.

- In testis, the innermost layer is tunica vasculosa
- The testes are normally 6 cm in length and 4 cm in width. A normal testis volume is generally above 16 mL and averages 20 mL.
- In humans, interstitial tissue takes up 20% to 30% of the total testicular volume, whereas germ line cells constitute the remainder (70% - 80%).
- Arterial supply: testicular artery
- of veins, which empties the venous blood come from the hilum and create the from the testis.
- from the internal spermatic or gonadal composed near the superior aperture of veins. These veins are spared during the pelvis/pelvic inlet. The right ovarian varicocele ligation surgery.

Lymphatic drainage: Drain into bilateral preaortic and a para-aortic groups of lymph the ovary follow the ovarian vein and drain nodes at the level of the lumbar vertebra.

#### **Ovaries**

surrounded by:

- · Posteriorly by the ureter and internal iliac vessels.
- Anteriorly by the external iliac vessels.
- . Inferiorly by the uterine tubes (in the complimentary margin of the broad ligament)

Nerve supply: The ovary is innervated by the postganglionic sympathetic (T10, T11) and parasympathetic (S2, S3, S4) fibers, originated from abdominal autonomic plexuses.

Arterial supply: The ovary is primarily supplied by an ovarian artery, which originates from the aorta at the level of L1 vertebra.

 Venous drainage: The pampiniform plexus
 Venous drainage: the veins of the ovary pampiniform plexus around the ovarian . The pampiniform plexus of veins forms artery, from which a single ovarian vein is vein empties into the inferior vena cava while the left ovarian vein empties into the left renal vein.

Lymphatic drainage: The lymphatics from into the pre-aortic and bilateral paraaortic lymph nodes

# Pelvis and Perineum

### **Ductus (Vas) Deferens**

- The terminal part of the vas deferens is dilated to form the ampulla of the vasa deferens
- . The inferior end of ampulla narrow down and joins the duct of seminal vesical to form the ejaculatory duct
- It passes lateral to the inferior epigastric artery at deep inguinal ring and cross ureter in the region of ischial spine
- Pseudostratified Epithelium: columnar epithelium
- Thick three layers of smooth muscle coats: inner, outer, longitudinal, middle circular
- Function: deliver spermatozoa from tail of Epididymis to the ejaculatory duct

### Seminal vesical

- Inferiorly each seminal vesical narrow and joins the vas deferens of the same side and form the ejaculatory duct
- pseudo-Epithelium: columnar stratified epithelium, with the height that varies with testosterone level, it lines the extensively folded mucosa
  - Function: the seminal vesical secrete a yellow, viscous fluid containing substances that activate sperm (e.g. fructose, prostaglandin vitamin C), this fluid constitute about 70% of the human ejaculate
  - The seminal vesicles are extremely resistant to disease.

### **Ejaculatory duct**

- Formed by the union of the vas deferens and the duct of seminal vesicle
- Epithelium: Simple columnar epithelium
- It lacks a muscular wall
- Function: deliver spermatozoa, seminal fluid to the prostatic urethra at colliculus seminalis

### Vasa deferens + Seminal vesical + Ejaculatory duct and Prostate

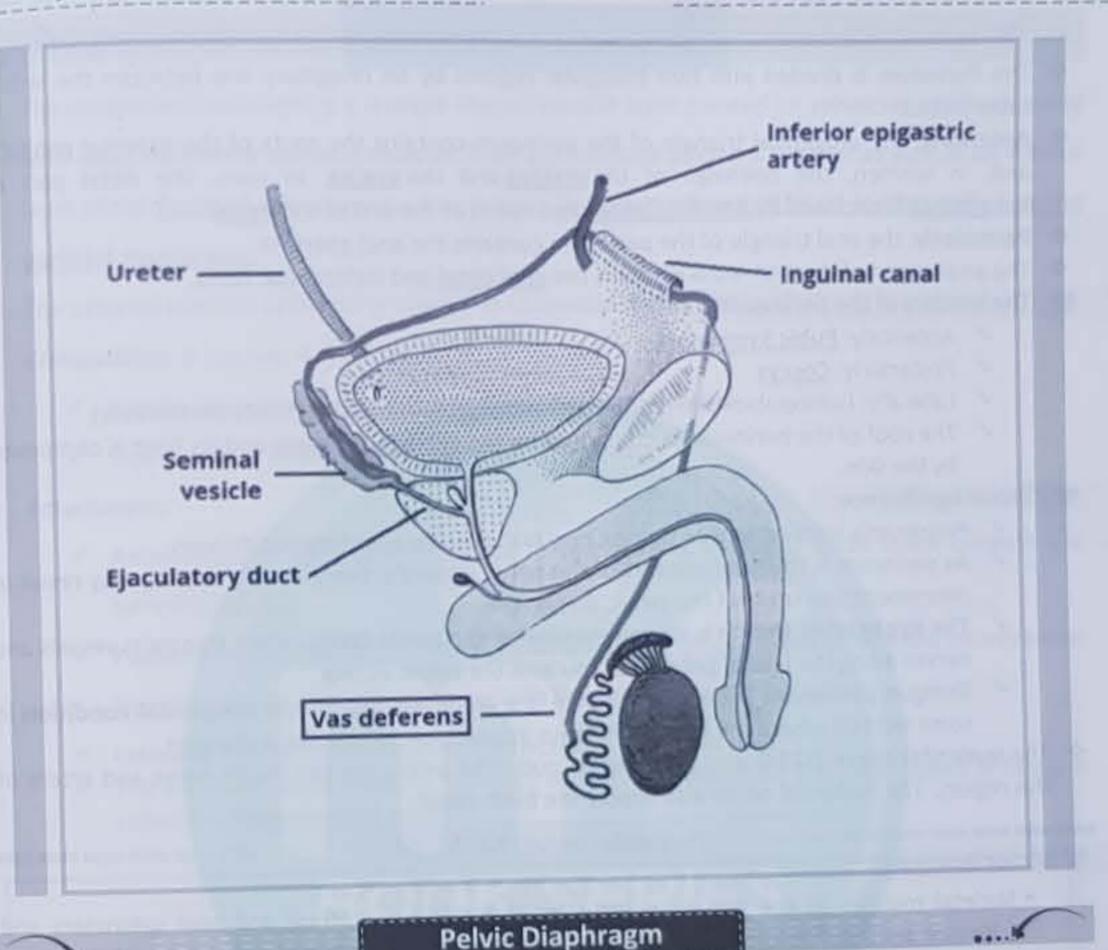
- Lymph drainage of all ——Internal iliac node
- Venous drainage of all-----Internal iliac vein
- All supplied by: inferior vesical artery and middle rectal artery

### **Epididymis**

- NAME AND POST OFFICE ADDRESS OF THE OWNER, WHEN Anatomically, the epididymis is divided into three regions: the caput, the corpus, and the cauda epididymis. On the basis of Histologic criteria, each of these regions can be subdivided into distinct zones separated by transition segments.
- The epididymis serves to transport sperm, store it, increase fertility, and promote motility maturation. Epididymal function is temperature and androgen (DHT) dependent. Sperm fertility maturation is achieved at the level of the late corpus or early cauda epididymis.

### Chapter 13

Pelvis and Perineum



- A muscular partition between the <u>true pelvis</u> and the <u>perineum</u> is known as the pelvic diaphragm.
- A gutter-shaped pelvic floor is created by this diaphragm. It's created by the large levator ani and small coccygeus muscles of 2 sides and their covering fasciae.
- Its structure is incomplete anteriorly to allow passage of urethra in the males and vagina in the females.
- Function:
  - ✓ The pelvic diaphragm gives main support to the pelvic viscera and has sphincteric actions. on the rectum and vagina.
  - ✓ The intra-abdominal pressure during defecation, micturition, and parturition is raised with its help.
- Clinical significance:
- ✓ Injury of pelvic diaphragm: The pelvic diaphragm could be injured (tearing of perineal body) during challenging childbirth. As a consequence, it becomes weak and can no longer provide adequate support to the pelvic viscera. This may result in uterine Prolapse and rectal Prolapse.
  - ✓ Dynamic support of the uterus is provided by the pelvic diaphragm

Perineum

- The Perineum is divided into two triangular regions by an imaginary line between the ischia
- \* Anteriorly, the urogenital triangle of the perineum contains the roots of the external genitalia and, in women, the openings of the urethra and the vagina. In men, the distal part of the <u>urethra</u> is enclosed by <u>erectile tissues</u> and opens at the end of the <u>penis</u>.
- Posteriorly, the anal triangle of the perineum contains the anal aperture.
- The anal region of the perineum contains the <u>anal canal</u> and Ischiorectal fossa.
- The borders of the perineum are:
  - ✓ Anteriorly: Pubic Symphysis
  - ✓ Posteriorly: Coccyx
  - Laterally: Ischiopubic rami (anteriorly) and sacrotuberous ligaments (posteriorly).
  - ✓ The roof of the perineum is composed by the pelvic diaphragm and its floor is composed by the skin.

### Clinical significance:

- ✓ Perineum's involvement or tearing may occur during spontaneous delivery
- ✓ As perineum is the final support of the pelvic viscera's, therefore, its tearing may result in permanent weakness of the pelvic diaphragm.
- ✓ The Hypogastric sheath is a condensation of the pelvic fascia, which transmits vessels and nerves along the lateral pelvic wall towards the pelvic viscera
- Shotgun perineum: Shotgun perineum is a medical slang for the congenital condition some women where the vagina and anus appear side by side like a shotgun
- . The pudendal nerve (5234) and the internal pudendal artery are the major nerve and artery of this region. The Pudendal nerve also supply the birth canal

#### Pudendal nerve: S2, S3, S4

### Motor function

 Skeletal muscles in the perineum including the external urethral and anal sphincters and levator ani (overlaps in the supply of the levator ani and external sphincter with branche directly from the ventral division of S4).

### Sensory (cutaneous) function

· Most of the skin of the perineum. Supply urogenital triangle

### **Urogenital Triangle**

- The urogenital triangle of the perineum is the anterior half of the perineum and is oriented in the horizontal plane. The urogenital region is triangular in shape. It is composed of the roots of the external genitalia and the openings of the urogenital system.
- The urogenital triangle of the perineum is defined as:
  - Laterally by the ischiopubic rami.
  - ✓ Posteriorly by an imaginary line between the ischial tuberosities.
  - ✓ Anteriorly by the inferior margin of the Pubic Symphysis.
- As with the anal triangle, the roof or ceiling of the urogenital triangle is the levator ani muscle Unlike the anal triangle, the urogenital triangle contains a strong fibromuscular support platform the perineal membrane and deep perineal pouch, which is attached to the pubic arch. Anterio extensions of the ischio-anal fossa occur between the deep perineal pouch and the levator muscle on each side.

### Chapter 13

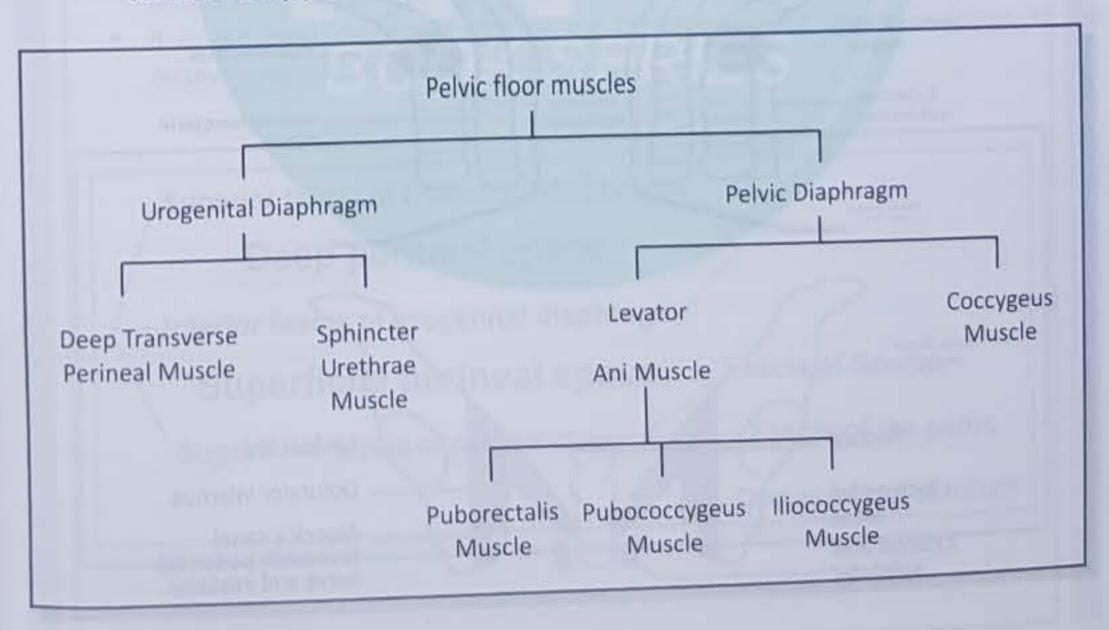
**Pelvis and Perineum** 

### **Urogenital Diaphragm**

- . The urogenital diaphragm is a triangle shaped muscle layer created by sphincter urethrae along with deep transverse perineal muscles. They are confined among a superior as well as an inferior layer of the fascia of the urogenital diaphragm. The inferior layer of fascia is often called as the perineal membrane.
- The external urethral sphincter is present in urogenital diaphragm
- Composition: it has two fasciae called
  - ✓ Inferior layer of the diaphragm or the perineal membrane
  - ✓ Superior layer of the diaphragm

#### Attachment:

- ✓ Anteriorly, the two layers of fascia merge, leaving behind a small space beneath the Symphysis pubis.
- Posteriorly, the two layers of fascia fuse with each other as well as with the membranous layer of the superficial fascia along with the perineal body.
- Laterally, the layers of fascia are connected to the pubic arch.
- The confined space which is enclosed among the superficial and deep layers of fascia is called the deep perineal pouch.



**Ischiorectal Fossa** 

### W Boundaries:

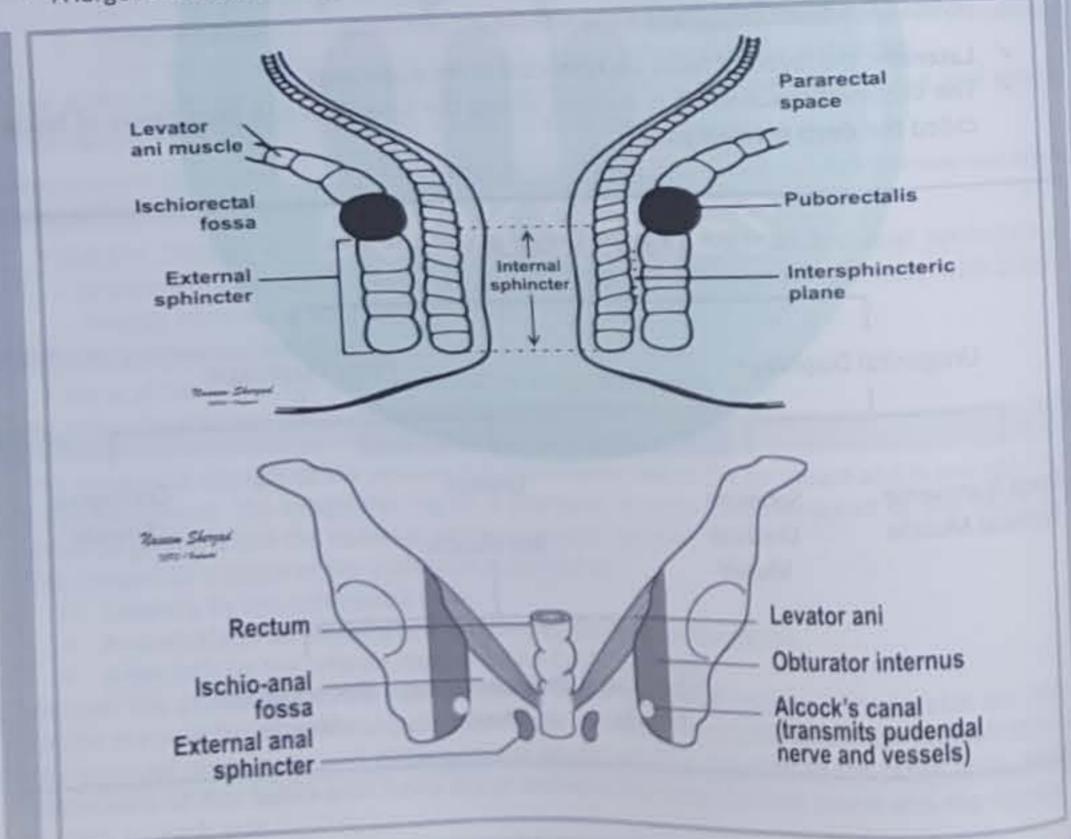
- -ischium, obturator internus muscle, and the sacrotuberous ligament · Base-Lateral wall--
- -levator ani muscle Medial wall-----

### tontents:

- Pudendal nerve and its branches
- Internal pudendal vessels
- Pudendal canal and its content
- Ischiorectal pad and fat
- The pudendal (Alcock's) canal is a sheath in the <u>lateral wall of the Ischiorectal</u> fossa.
  - ✓ It conveys the <u>pudendal nerve</u> and internal pudendal vessels from the lesser sciatic note to the deep perineal pouch

### Function and importance:

- . The ischio-anal fossa allows movement of the pelvic diaphragm and expansion of the and canal during defecation.
- A large fascia-lined, wedged-shaped space on each side of the anal canal



Chapter 13

**Pelvis and Perineum** 

### Superficial Perineal Pouch and Deep Perineal pouch

### 1) Superficial perineal pouch:

#### Content:

- Structure forming root of penis/clitoris
- Bulbospongiosus muscle and ischiocavernosus muscle
- Superficial transverse perineal muscle
- Perineal branch of the pudendal nerve
- Perineal body
- Greater vestibular gland or Bartholin glands

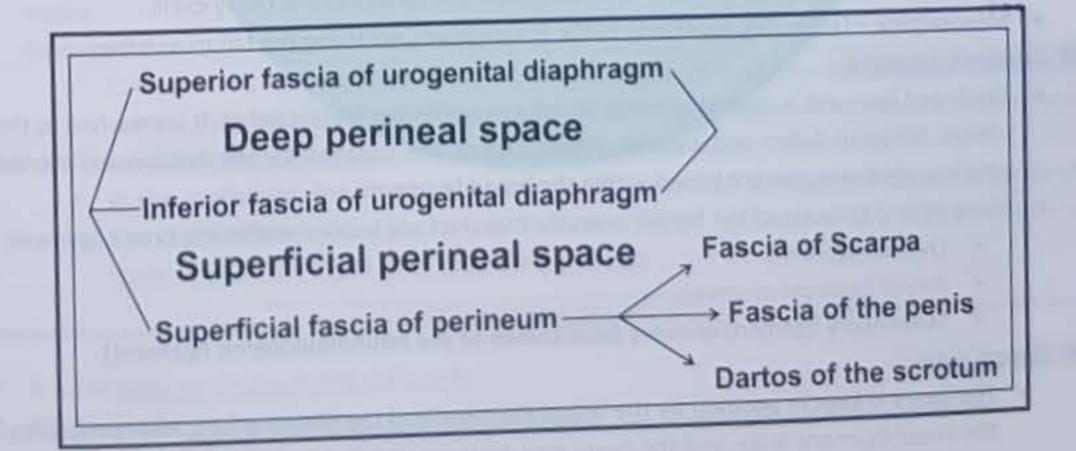
### 2) Deep perineal pouch

#### Contents:

- Membranous part of the urethra
- Sphincter urethra muscle
- Deep transverse perineal muscle
- Internal pudendal vessels and its branches
- Dorsal vein of clitoris/penis
- Bulbourethral gland, also called a Cowper's gland

### 3) Rectouterine pouch:

- The Rectouterine pouch, also known as the rectovaginal pouch or pouch of Douglas, is an extension of peritoneum between the posterior wall of the uterus and the rectum in females.
- . It is the most dependent part of the peritoneal cavity and is analogous to the rectovesical pouch in males.



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**Pelvis and Perineum** 

Pelvis and Perineum

# Ligaments of the Female Reproductive Tract

The ligaments of the female reproductive tract are a series of structures that support the internal

female genitalia in the pelvis.

The ligaments of the female reproductive tract can be divided into three categories:

- Broad ligament a sheet of the peritoneum, associated with both the uterus and ovaries.
- Uterine ligaments ligaments primarily associated with the uterus.
- Ovarian ligaments ligaments primarily associated with the ovaries.

Collectively, these ligaments are tough and non-extensible. They act to support the female viscen and provide a conduit for neurovascular structures.

### **Broad ligament**

The broad ligament is a flat sheet of the peritoneum, associated with the uterus, fallopian tubes and ovaries. It extends from the lateral pelvic walls on both sides, and folds over the internal female genitalia, covering their surface anteriorly and posteriorly.

Anatomically, the broad ligament can be divided into three regions:

### **Subdivisions**

- Mesometrium: Surrounds the uterus and is the largest subsection of the broad ligament.
   runs laterally to cover the external iliac vessels, forming a distinct fold over them. The mesometrium also encloses the proximal part of the round ligament of the uterus.
- Mesovarium Part of the broad ligament associated with the ovaries. It projects from the
  posterior surface of the broad ligament and attaches to the hilum of the ovary, enclosing a
  neurovascular supply. It does not, however, cover the surface of the ovary itself.
- Mesosalpinx Originates superiorly to the mesovarium, enclosing the fallopian tubes.

### M Anatomic relations

- The broad ligament is related to many structures within the female pelvis. It is attached to the uterus, fallopian tubes and ovaries. These organs are supplied by the ovarian and uterint arteries, which are also contained within the broad ligament.
- Three other ligaments of the female reproductive tract are located within the broad ligament
  - ✓ Ovarian ligament
  - ✓ Round ligament of uterus
  - ✓ Suspensory ligament of ovary (also known as the infundibulopelvic ligament)

### M Clinical notes:

The ovary is kept in position by the broad ligament and the Mesovarium. After pregnance
the broad ligament is lax, and the ovary may prolapse into the Rectouterine pouch. In the
circumstances, the ovary may be tender and cause discomfort on intercourse

### The Ovarian Ligament

The ovarian ligament is attached to the ovary inferiorly. It connects the ovary to the side of the uterus. Structurally, it is a fibrous band of tissue that lies within the broad ligament. It joins the uterus just below the origin of the fallopian tubes.

### The Suspensory Ligament of Ovary

The suspensory ligament of ovary extends outwards from the ovary to the lateral abdominal wall. It consists of a fold of peritoneum, thus some sources consider it to be part of the broad ligament. The function of this ligament is to contain the ovarian vessels and nerves (ovarian artery, ovarian vein, ovarian nerve plexus and lymphatic vessels).

### Round ligament of Uterus

- Extend from Superolateral angle of uterus pass through deep and superficial inguinal ring and attach or terminate on labium majora
- \* Both intra-pelvic and extra-pelvic

----

- Keep the uterus Anteverted and Anteflexed
- Considerably stretch during pregnancy
- . Carcinoma uterus and cervix spreads to labia majora via round ligament of uterus
- The round ligament is a remnant of the embryonic Gubernaculum.

### ·...

Posterior Fornix of Vagina, Ischial spine and Perineal body

### Posterior fornix of vagina

- Not supplied by pudendal nerve but supplied by inferior hypogastric plexus
- Abscess in Rectouterine pouch or pouch of Douglas can be drained through posterior fornix of vagina
- Culdocentesis:
  - Culdocentesis is a procedure involving the extraction of fluid from the pouch of Douglas. It can be one diagnostic technique used in identifying pelvic inflammatory disease and ruptured ectopic pregnancies that cause hemoperitoneum.
  - ✓ In the procedure, the Pouch of Douglas is often reached through the posterior fornix of the vagina. The process of creating the hole is called "colpotomy" if a scalpel incision is made to drain the fluid rather than using a needle.

### Ischial spine

- It is the bony landmark during child-birth
- It is the landmark for pudendal anesthesia (stage-II)
- . It is a landmark for Bishop scoring

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- Inverted Ischial spine is seen in the anthropoid pelvis
- Ureter enter bladder at the Ischial spine

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OF REAL PROPERTY AND PERSON NAMED IN

## Pelvis and Perineur

### Chapter 13

### Perineal body

- The perineal body is a pyramidal fibromuscular mass in the middle line of the perineum at the anal triangle. It is found in beautiful. The perineal body is a pyramidal model and the anal triangle. It is found in both males and
- Situation: About 1.25 cm in front of the anal margin and close to the penis
- Function—it is very important in females for the support of the pelvic organs.

## Muscle forming perineal body: BLESSeD

- ✓ Bulbospongiosus
- ✓ Levator ani
- ✓ External anal sphincter
- ✓ Superficial transverse perinei
- ✓ Sphincter urethra
- ✓ Deep transverse perinei

### M Clinical consideration:

- ✓ There is no attachment or insertion of ischiocavernosus muscle on perineal body
- ✓ The Perineal body can also be disrupted by trauma, inflammatory disease and infection. which may produce fistula that connected to the vestibule of the vagina.
- ✓ In women, it acts as a tear-resistant body between the vagina and the external and sphincter, supporting the posterior part of the vaginal wall against Prolapse. In the male it lies between the bulb of the penis and the anus.
- Childbirth can lead to damage (stretching/tearing) of the perineal body, thus leading to possible Prolapse of pelvic viscera.
- Episiotomy: An episiotomy is a planned incision made in the perineum in posterolatera direction by cutting the tissue between the vaginal opening and the anus during childbirth. This is done to enlarge the vaginal opening to facilitate the childbirth thereby preventing the tear of the perineal body.
- ✓ The main disadvantage of midline episiotomy is the increased risk for the tear this extend into or through the anal muscle that's why obstetrician reluctant for media episiotomy due to risk of the external anal sphincter injury
- The Muscles which cut in Midline Episiotomy are, Bulbospongiosus muscle and Superficial transverse perineal muscle

### Diameters at Different Levels of True Pelvis in a Gynaecoid pelvis

Levels	Anteroposterior diameter(cm)	Transverse diameter(cm)
Pelvic inlet	11.5 (10 X 11.5= 115mm)	13.5 (10 X 13.5= 135mm)
Pelvic cavity	13.0 (10 X 13= 130mm)	12.5 (10 X 12.5= 125mm)
Pelvic outlet	13.5 (10 X 13.5= 135mm)	11.5 (10 X 11.5= 115mm)
Gynaecoid pelvis	<ul> <li>It typical female pelvis</li> <li>Ideal for vaginal delivery</li> <li>Subpubic arch is wide—90 or</li> <li>Found in 80% of Asian word</li> <li>Good sacral curve</li> </ul>	degree

Chapter 13

**Pelvis and Perineum** 

Mnemonic: ---GAAP----G (50%, MC), A (25%), A (20%), P (rarest)

* Characteristic	<u>G</u> ynaecoid	<u>A</u> nthropoid	<u>A</u> ndroid	<u>Pl</u> atypelloid
General features	Typical female pelvis		Typical male pattern	Ricketic pattern
Pelvic inlet	Oval-shape More transverse diameter than Anteroposteri or diameter	Oval in shape Anterior posterior diameter is more than transverse diameter Often high angle of inclination	Triangular/hea rt - shaped Reduced true conjugate	Flattened oval Transverse diameter is much more than Anteroposterior diameter Reduced true conjugate
Pelvic cavity	Rounded in shape	Rounded in shape Sidewalls are divergent	Sidewalls are convergent (funneling) Ischial spine are prominent leading to decreased inter-ischial diameter	Sidewall are divergent, sacrum flattened or angulated
Pelvic outlet	Oval in shaped Anterior posterior diameter is more than transverse diameter	Oval in shape Anterior posterior diameter is more than transverse diameter	Oval in shape Narrow subpubic angle	Wide subpubic angle
Clinical Significance	Most suitable pelvis for vaginal delivery	Head engages with sagittal suture in Anteroposterior diameter leading to delayed engagement of the head	pelvis Account for a larger proportion of difficult	engagement of head leading to a high incidence

## Female Reproductive System

# M Paramesonephric duct(or Müllerian ducts):

- In the absence of a Y chromosome and in the presence of 2 X chromosomes, ovaries develop the mesonephric ducts regress, the Paramesonephric ducts develop.
- The superior end of these ducts opens into the future peritoneal cavity. The lower end becomes the uterus and uterine tubes
- \* Counterpart of Müllerian ducts-Rete testis (It is the counterpart of the rete ovarii in females)
- Counterpart of Müllerian tubercle ------Seminal colliculus
- Failure of fusion of Müllerian ducts result in------Bicornuate uterus
- Paramesonephric ducts regress in the male by------MIF
- Paramesonephric ducts vestigial remnants
  - ✓ Female------Hydatid of Morgagni
  - ✓ Male———Appendix testis
- · MIF:
  - Anti-Müllerian hormone (AMH), also known as Müllerian inhibiting substance (MIS) or factor (MIF), is a member of the transforming growth factor-β (TGF-β) secreted essentially by fetal and prepubertal Sertoli cells and to a lesser amount by granuloss cells of small follicles.

### Male Reproductive System

#### Mesonephric duct

- The mesonephric duct (also known as the Wolffian duct, Leydig's duct or nephric duct)
- In the presence of a Y chromosome, testes develop and produce an inducer substance stimulating the development of the mesonephric ducts into the male genital ducts : SEED
  - ✓ Seminal vesicle, Ejaculatory duct, Epididymis, Ductus deferens
- Androgens from the fetal testes stimulate the development of the indifferent external genitals into the penis and scrotum. A suppressor substance (müllerian inhibiting substance), also produced by the testes, inhibits the development of the Paramesonephric ducts.
- Vestigial remnants in female
  - ✓ Mesonephric duct:
    - Appendix vesiculosa
    - o Gartner duct
  - ✓ Mesonephric tubules
    - o Epophoron
    - o Paraphoron
- Vestigial remnants in Male
  - ✓ Duct ———Appendix Epididymis
  - ✓ Tubules-----Parardidymis

### **Urogenital Sinus form**

- Prostate
- Bulbourethral gland
- Great vestibular gland

**Pelvis and Perineum** 

### External Genital Organ Development

Mesoderm around the cloaca membrane cause overlying ectoderm to form three structure

- Phallus:
  - ✓ In male form penis, corpora cavernosum and spongiosum
  - ✓ In female form Glans clitoris
- Urogenital fold;

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- ✓ Labia minora and ventral part of the penis
- Labioscrotal swellings or genital swelling:
  - ✓ Labia majora + Mons pubis and scrotum
- Genital tubercle:
  - ✓ Glans of penis in the male and clitoris in the female
- The vagina develops from the vaginal plate derived from the urogenital sinus, and the indifferent external genitalia develop into the clitoris and labia
- The scrotum in the male is developmentally homologous to labia major in female

### **Congenital Abnormalities**



#### Mypospadias:

- It is the most common congenital malformation of the urethra
- Occur when urogenital fold fail to fuse
- External orifice opening on the ventral (underside) surface of the penis
- It is classified according to the position of the meatus, glandular is the most common and does not require treatment
- Avoid circumcision in patient of Hypospadias as the prepuce may be used in the procedure to correct Hypospadias

### **W** Epispadias

- Occur due to abnormal positioning of the genital tubercle
- External orifice opening on the dorsal surface
- Associated with exstrophy of the bladder

### Pelivureteric junction (PUJ) obstruction:

- It can be congenital or acquired with a congenital PUJ obstruction being one of the commonest causes of antenatal Hydronephrosis.
- PUJ obstruction is most commonly unilateral (and cause unilateral Hydronephrosis) but is reported to be bilateral in ~30% (range 10-49%) of cases
- Many cases are asymptomatic and identified incidentally when the renal tract is imaged for other reasons. When symptomatic, symptoms include recurrent urinary tract infections, stone formation and even a palpable flank mass.
- Ultrasound will often show a dilated renal pelvis with a collapsed proximal ureter

### M Posterior Urethral Valve (PUV)

- Posterior urethral valve are congenital membrane-like structures located in the distal
- The Obstructive congenital defect is caused by a malformation of the posterior urethra
- PUV is the most common cause of severe types of urinary tract obstruction in children.

### Polycystic Ovarian Syndrome (PCOS)

- PCOS is the most common cause of secondary amenorrhea and is responsible for 75-80% of anovulatory subfertility
- . It is the most common endocrine disorder in female
- . Up to 70 percent of women with PCOS have insulin resistance, meaning that their cells can't use insulin properly
- There is Increase risk of diabetes mellitus
- Clinical features:
  - ✓ Oligomenorrhoea/amenorrhea
  - ✓ Infertility
  - ✓ Hirsutism——PCOS is the Most common cause of Hirsutism in female
  - √ Obesity
  - ✓ Acanthosis nigricans

#### Diagnosis:

- ✓ Elevated testosterone level
- ✓ Decrease sex hormone-binding globulin
- ✓ Elevated LH levels
- ✓ Increase LH: FSH ratio-----2.5:1

## Menopause

- There is a Decrease of estrogen and Increase FSH and LH level in menopause
- There is Unresponsiveness of ovary in menopause
- Low estrogen level leads to:
  - ✓ Women are put at increased risk of cardiovascular disease
  - ✓ Osteopenia and osteoporosis
  - ✓ Hot flushes
  - ✓ Mood swing
  - √ Headache
- In postmenopausal women, osteoporosis is due to a decrease in estrogen level
- Postmenopausal women with bone pain due to decrease estrogen level are treated with SERM
- The most common cause of postpartum hemorrhage is uterine atony

# Cervix

### Cervical Intraepithelial Neoplasia (CIN)

The pre-invasive disease of the cervix is called cervical intraepithelial Neoplasia (CIN)

· Classification

- I. Histological classification/on biopsy
  - CIN1: Mild dysplasia, 60% spontaneous regress
  - CIN 2: Moderate dysplasia, 40% spontaneous regress
  - CIN3 or carcinoma in Situ: Severe dysplasia, 30% spontaneous regress

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CHAPTER

## PATHOLOGY AND PHYSIOLOGY OF MALE AND FEMALE GENITAL SYSTEM

# Table with some high yield points

Disease	High yield
Discuse	Ovarian Fibroma
• Meig's syndrome	<ul> <li>Ascites</li> <li>Right-sided pleural effusion</li> </ul>
❖ Yolk sac tumor	Schiller Duval body     Resemble primitive glomeruli
	Reinke crystal
❖ Malacoplakia	<ul> <li>Michaelis Gutmann body</li> <li>laminated mineralized concerts resulting from deposition of calcium in enlarged lysosome which is typically present in macrophage</li> </ul>
❖ Invasive lobular carcinoma	Bull's eye appearance     Single-layer of tumor cell in a linear of concentric fashion
❖ Granulose theca cell tumor	Call Exner body
❖ Embryonal Rhabdomyosarcoma	Tennis racket
→ HELLP Syndrome	Hemolysis, Elevated Liver Enzyme Level     and Low Platelet

#### Infertility

- The most common cause of subfertility is ------Anovulation or absence of ovulation
- The most common cause of congenital male infertility or the most common testicular cause of infertility and Azoospermia is------ Cryptorchidism
- The most common reversible cause of male infertility is——Varicocele
- The most common cause of female infertility-
- The most common cause of premature ovarian failure-
- The most common site for fertilization is-

- -- PCOS
- -Autoimmune disease
- -Fallopian tube

#### Pathology & Physiology of Male & Female Genital System Chapter 14

# ii. Cytological classification/on pap smear

- . LSIL: CIN1
- HSIL: CIN2 and CIN3

## \* Association with Human papilloma virus:

- High risk (malignant): HPV 16 (most prevalent type 59%) & HPV 18 (12%)
- Low risk (benign): HPV 6 and HPV 11

### Screening test:

### > PAPANICOLAOUS (PAP) smear:

- PAP smear is the most successful and effective screening test in medical history.
- Only screening test with 70% to 80% reduction of death rate.
- Cells are scraped from transformation Zone and examined microscopically

## \* What is transformation zone(T-zone ) what is its importance:

- The area where the squamous epithelium is replaced by columnar epithelium and then by squamous epithelium again is called transformation zone.
- It is important because 95% of cancer and dysplasia occur in this area.

### Invasive carcinoma of the cervix

- Classification: All of the following are caused by HPV
  - √ Squamous cell carcinoma: 75%
  - Adenocarcinoma and mixed Adenocarcinoma: 20%
  - ✓ Small cell neuroendocrine carcinoma: less than 5 %
- Develop in the transformation zone
- Tumor encircling the cervix and penetrating into the underlying stroma produce a Barrel Cervix which can be identified by direct palpation.
- The disease is said to be more common in married than unmarried.
- Smoking, Immunosuppression (like using immunosuppressant drugs) and HPV increase the risk of cervical carcinoma.

# What is the difference between endometriosis and Adenomyosis?

Endometriosis:

## Endometriosis is defined as a condition in which tissue structurally and functionally similar to the endometrium is present outside the uterine cavity for which ovaries are the commonest

- site When the ovaries involved the lesion may form blood-filled cyst that turns brown (chocolate cyst) as the blood ages.
- The diagnosis of chronic endometriosis requires the presence of the plasma cell.

### 2) Adenomyosis:

Adenomyosis is defined as a condition in which tissue structurally and functionally similar to the endometrium is present in the myometrium.

### Abnormal Uterine Bleeding: cause may be known or unknown



- On the basis of etiology divided into two major group
  - > Abnormal uterine bleeding due to an identifiable organic cause
  - > Dysfunctional uterine bleeding (DUB): DUB can be defined as, abnormal uterine bleeding of any type in the absence of recognizable pelvic pathology, drug therapy, pregnancy or general medical/bleeding disorders.

### Ectopic pregnancy

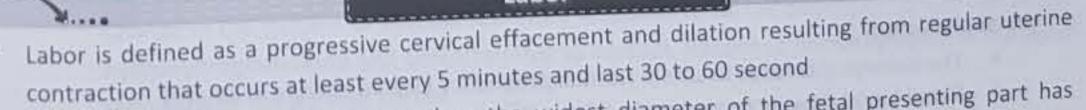


- Ectopic pregnancy is defined as the implantation of a fertilized ovum at a site other than the uterine cavity.
- The fallopian tube is the commonest site of ectopic pregnancy accounting for 95% of ectopic pregnancy (remember for endometriosis commonest site is ovary, don't mix both). Within the fallopian tube, ampulla is the most common site. This type of pregnancy is called the tubal pregnancy.
- Ovary is the second most common site, abdominal cavity is the 3<sup>rd</sup>
- Ovary is the least common site for ectopic pregnancy according to CPSP key
- Tubal rupture is the most common complication of the tubal pregnancy.
- Pelvic inflammatory disease is the most common etiologic factor of tubal pregnancy.
- Methotrexate can be used as a medical treatment for un-ruptured ectopic pregnancy
- Laparoscopy is the best method for diagnosing ectopic pregnancy
- Hysterosalpingography is more accurate than MRI in the blocked fallopian tube
- There is no metastasis occur in ectopic pregnancy

### Important for BCQs



- The <u>commonest</u> form of primary vaginal cancer is <u>squamous cell carcinoma</u>, commonly occur in the upper part of the vaqina and human papilloma virus (HPV) has been suggested as a possible cause. On examination, Seen on the posterio-superior aspect of the vagina as plaques like lesion
- The most common Gynecological malignancy is <u>Endometrial Carcinoma followed by ovary, cervix</u> and vulva.
- The cause of death in carcinoma cervix is renal failure.
- Ovarian metastasis early occurs to, peritoneum 85%, omentum 70% & liver 35%.



- Engagement: Engagement occurs when the widest diameter of the fetal presenting part has passed through the pelvic inlet
- There are four stages of labor each of which is considered separately
- The head of the fetus is the largest and least compressible part of the fetus

### Chapter 14

# Pathology & Physiology of Male & Female Genital System

- Labor initiated by------fetal cortisol/ACTH
- Abdominal muscle contractions is most important factor in the 2<sup>nd</sup> stage of labor
- The Substance which helpful in the 2<sup>nd</sup> stage of labor is oxytocin
- During pregnancy, HIV transmission occurs mostly during labor
- Sequences of stages of delivery: engagement, flexion, extension, descent, extension, restitution anterior shoulder delivery, posterior shoulder delivery

# Physiological Changes in Pregnancy

- Increase serum ALP: placental origin
- One uterine contraction squeeze 300-500ml blood into the maternal circulation during the labor
- Eversion of endocervical epithelium is a physiological change in pregnancy
- Mother will felt the fetal movement in 5th months of pregnancy
- Normal fetal heart rate is 120-160 beat per minute
- At the end of the pregnancy, the uterus is most sensitive to oxytocin which having receptor or myometrium and endometrium
- Fetus start movement at 8 weeks (2months) but felt by mother at 20 weeks (5 months)
- Mother-child bonding -----FosB gene
- Antibody secreting plasma cell in endocervix vagina fallopian tube is -----70%

### Cardiovascular changes

- Cardiac output is highest shortly after delivery
- Cardiac output raised: 30%-50%
- Stroke volume raised: 10%
- Dilutional anemia, Hb decreased due to a greater increase in plasma volume

### Hormonal changes during pregnancy:

- The thyroid gland undergo moderate enlargement during pregnancy
- Plasma folate concentration decreased
- Prolactin and corticosteroid concentration increases
- TSH decreases in early pregnancy
- Glycosuria is normal during pregnancy
- Hypercholesteremia occur in pregnancy
- Glycogen synthesis and storage by the liver increase and Gluconeogenesis is inhibited
- In the context of maternal lipids metabolism, the most dramatic lipid changes in pregnant is the rise in fasting triglyceride concentration
- Glucose intolerance: Increased human placental lactogen inhibit the sensitivity peripheral tissue to insulin, Insulin resistance develop
- Carbohydrate metabolism: pregnancy is characterized by mild fasting hypoglycemic greater suppression of glucagon

### Renal physiology:

- The kidneys increases in size in normal pregnancy (1-2cm change in length)
- Renal blood flow increased up to 80% in 2<sup>nd</sup> trimester of pregnancy
- Pregnancy causes compensated respiratory alkalosis with chronic losses of ren bicarbonate
- Renin level elevated throughout the pregnancy

#### Chapter 14

### Pathology & Physiology of Male & Female Genital System

Increase GFR and creatinine clearance

### Oxygen consumption and ventilation:

- √ Total body oxygen consumption increase about 15 to 20% in pregnancy.
- √ The rise in minute ventilation reflects an approximately 40% increase in tidal volume at term.
- ✓ Mild respiratory alkalosis: due to stimulation of respiratory center by estrogen and progesterone
- ✓ Increase in respiratory rate is due to-----increase progesterone level
- ✓ Decreased PCO2, increased PO2, Ph alter little, increased bicarbonate excretion
- ✓ Increase in 2-3 DPG within maternal erythrocyte causes a shift of oxygen curve to the right in mother and left in the fetus
- ✓ Oxygen consumption increase by about 45ml/min during pregnancy
- ✓ Pregnancy is characterized by hyperventilation and associated respiratory alkalosis
- ✓ Increased minute ventilation, increased tidal volume, decreased residual volume and FRC. Vital capacity unchanged or slightly increased

### Trimester of pregnancy:

#### > First trimester:

- Corpus luteum is responsible for the production of estradiol and Progesterone
- The Peak level of HCG occur at gestational week 9, then decline

### > 2<sup>nd</sup> and 3<sup>rd</sup> trimester:

- Progesterone produce by-----Placenta
- Estrogen produce by------Fetal adrenal gland and placenta
- The major placental estrogen is estriol
- > Pregnancy with recurrent abortion-----anti-phospholipids syndrome
- > The majority of postpartum hemorrhage (75-80%) are due to uterine atony, trauma during delivery is the 2<sup>nd</sup> most common cause of postpartum hemorrhage

### **Normal Pubertal Landmarks**

- Complete puberty is characterized by the occurrence of all pubertal changes
  - ✓ The most common initial change is Thelarche (breast enlarging at age 0-10)
  - ✓ This is followed by adrenarche (pubic and axillary hair at 10-11), the appearance of pubic hair dependent on the secretion of adrenal androgens and is usually after Thelarche. Change in the pattern of adrenal secretory response to ACTH, disproportionate rise of 17hydroxypregnenolone and DHEA relative to cortisol. Response primarily occur in the zona reticularis of the adrenal cortex
  - ✓ Maximal growth rate occurs at age 11 and 12
  - Finally, the last changes is menarche (onset of menses at the age of 12-13)
- The onset of puberty is due to pulsatile GnRH from the pituitary gland

Pathology & Physiology of Male & Female Genital System

## Rate and Ratio

### Perinatal period:

From 28<sup>th</sup> week of gestation to first 7<sup>th</sup> day of life

### · Perinatal mortality rate:

 Number of stillbirth and deaths in the first week of life per 1000 total births OR in sime. words stillbirth + early neonatal death/total birth multiply by 1000

### Stillbirth:

. It is the expulsion of the dead fetus after 28th weeks of gestation. So still birth is only include in perinatal mortality rate.

### \* Early neonatal death:

· An early neonatal death occur when the baby delivered alive, but who dies within fire week of life

#### Maternal Mortality Rate:

 Number of maternal death during a given time period per 1000 women of reproductive age (15-49 year) during the same period

### Maternal Mortality Ratio:

 Number of maternal death during a given time period per 1000 live birth during the same period

### Reproductive Health and Family Planning

- Pre-term: Baby born before 37 weeks of gestation
- Full term or term: Baby born between 37 and 42 weeks gestation
- Post-term: Baby born beyond 42 weeks of gestation
- Neonate: A baby is called neonate up to 4 weeks (28 days)
- Infant: Baby up to 1 year, Pre-school child: Below five years
- Child and adolescent: up to 16 years
- Primigravida: Primigravida is the first pregnancy
- Multigravida: Has been pregnant more than once
- Nulliparous women: Women that has not given birth previously
- Uterine size: Uterine size increase in pregnancy by 15 fold, 1000g which is only 60gm in non pregnant women.
- Weight gain in pregnancy: The accepted average total weight gain in healthy primigravida eatif without restriction is about 12.5 kg. The products of conception constitute only about 40% of the total maternal weight gain
- Clamping of cord: There is no need for immediate clamping of the cord and indeed about 80ml blood will be transferred from the placenta to the body before cord pulsation cease, reducing

chance of neonatal anemia and iron deficiency.

The Denominator of MMRatio, Infant Mortality Rate, and Neonatal Mortality Rate is PER 1000 LIVE BIRTHS.

The Denominator of Perinatal Mortality Rate, Fetal Mortality Rate is PER 1000 TOTAL BIRTHS.

### Safe motherhood: FACE

- √ Family planning
- ✓ Antenatal care
- ✓ Clean delivery
- ✓ Essential obstetric care

### . Contraception:

- ✓ The hormonal contraceptive method is the most commonly practiced temporary method. of contraception worldwide.
- ✓ IUCD is the second most commonly used method of contraception world wide
- √ Failure rate of IUCD is less than 1%
- Male condom is a commonly used method of contraception in Pakistan.
- ✓ In family planning there must be 2 year gap between two child
- ✓ Abnormal uterine bleeding is the most common complication of IUD use

### Contraindication of IUCD:

#### Absolute:

- o Active liver disease
- The Past or present history of Thromboembolism
- Suspected Pregnancy
- Pelvic inflammatory disease (PID)
- Undiagnosed Vaginal bleeding
- Cancer of breast and genitalia
- o Previous ectopic pregnancy
- Cardiac abnormalities and congenital hyperlipidemia

#### > Relative:

- o Anemia.
- o Hemorrhagic.
- History of PID since last pregnancy.
- Cervical discharge.
- Unmotivated female.
- o Menorrhagia
- IUCDs are not contraindicated in women with HIV positive status

Pathology & Physiology of Male & Female Genital System

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# Cryptorchidism (one or both) or Undescended Testis (UDT)

- It is associated with three to fivefold increases in the risk of cancer.
- It is most commonly transform into Seminoma.
- Treatment: Orchiopexy: mobilization of the testis and spermatic cord into scrotum usually performed before the age of one year.

## **Testicular Tumors Classification**

### Germ Cell Tumor

### Seminoma: Painless mass

- It is the most common testicular tumor
- It is <u>extremely radiosensitive</u>, having Good prognosis
- It metastases via LYMPHATICS route
- There are three subtypes:
  - ✓ Classic 80%
  - ✓ Anaplastic 10%
  - √ Spermatocytic 10%

### Non-Seminoma

- It metastases via HEMATOGENOUS route
- It is associated with raised HCG and AFP
- subtypes:

### @ Embryonal cell carcinoma

- Malignant tumor of immature, primitive cell that may form gland
- It is the most aggressive tumor
- Worse prognosis than Seminoma
- Hemorrhagic mass with necrosis

### P Yolk sac tumor

- Most common primary testicular neoplasm in children younger than 3 year of age
- o The germ cell tumor, which is common in infant and child is yolk sack tumor
- @ Teratoma
- Choriocarcinoma
- Leydig cell tumors
- Sertoli cell tumors

### Secondary tumors

Lymphoma, leukemia and melanoma are the most common malignancies that metastasis to the testicle.

### Classification of Ovarian Tumors

Surface Epithelial Tumor: 60-70 %

Over 90% of the malignant ovarian tumors are epithelial in origin while non-epithelial tumor accounts for less than 10% of the malignant tumor.

### 1) Serous Tumors

Chapter 14

- Serous cystadenoma is the commonest benign epithelial tumor.
- Serous Cystadenocarcinoma: Area of calcification called "Psammoama bodies" is a characteristic feature. CA-125 is a general ovarian cancer marker.

#### 2) Mucinous Tumors

- Mucinous cystadenoma is the second most common <u>benign</u> epithelial tumor.
- It is usually large, unilateral and multilocular and can weight up to 14 Kg
- Pseudomyxoma peritonei is a rare complication of mucinous cystadenoma usually of borderline malignancy.

### 3) Endometrioid Tumor

- The ovarian tumor which contains tubular glands similar to that of proliferative endometrium is called endometrial tumor
- Endometrioid carcinoma: Histologically, Endometrioid carcinoma is resembled endometrial carcinoma and 15% cases of Endometrioid carcinoma of the ovary are associated with endometrial carcinoma.

#### 4) Brenner

- It is composed of nests of benign transitional epithelium that found in urinary bladder surrounded by dense fibrous tissue.
- Coffee Bean nuclei on H & E staining

### 5) Clear Cell Tumors:

- Clear cell carcinoma has a characteristics microscopic appearance called "HOBNAIL Appearance"
- 6) Undifferentiated

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### Germ cell tumor: 15-20%

#### **Teratoma**

### A. Mature cystic teratoma (dermoid cyst):

- Dermoid cyst is the commonest benign germ cell tumor.
- It is the Commonest cyst seen during pregnancy
- Marked by the presence of mature tissues derived from all three germ cell layers (ectoderm, endoderm and mesoderm) but the derivatives of ectoderm are predominant.
- Thus it is lined with epithelial like epidermis and Contains sebaceous secretion, skin appendages, teeth, hair and nervous tissue. Endodermal derivatives include thyroid, bronchus and intestine and Mesoderm is represented by bones and smooth muscle

Pathology & Physiology of Male & Female Genital System

# Occasionally only a single tissue may be present when it is called Monodermal teratoms

- The classic example are Carcinoid and Struma Ovarii
- Struma Ovarii contains active thyroid tissue and the patient may present with the typical features of hyperthyroidism.
- B. Immature malignant teratoma

### Dysgerminoma:

- Uncommon tumor 2-5% of all primary malignant ovarian tumors
- Dysgerminoma is a solid tumor having a smooth or nodular surface and soft or rubben consistency.

## Endodermal sinus tumor (yolk sac tumor)

- Highly malignant tumor and common among children
- It is associated with raised in serum alpha-fetoprotein

### Choriocarcinoma

Rare tumor and characteristically associated with a raised level of hCG.

### Sex- cord-stromal tumors: 5-10%

#### i. Fibroma

. It is frequently associated with ascites, right-sided pleural effusion when called Meig's syndrome

### ii. Granulosa -Theca cell tumor

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- · May elaborate large amounts of estrogen (from thecal elements) and so may promote endometrial or breast carcinoma.
- Granulosa elements may recapitulate ovarian follicle as <u>Call-Exner bodies</u>.

### iii. Sertoli Leydig cell tumor

- Also called androblastoma, which is usually unilateral.
- 80% produce androgen which causing masculinization, while remaining are either estrogen producing or inert.

### Secondary Tumors

### Krukenberg tumor:

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- . Krukenberg tumor is not the primary ovarian tumors and the name given to ovarian malignancy where ovaries are secondarily involved in the metastasis from the primary tumo in the stomach.
- Krukenberg tumors are the most common metastatic ovarian tumors.
- Krukenberg tumor is usually bilateral.
- . Microscopically the cells have a "signet ring appearance" with the peripheral nucleus a mucoid spongy cytoplasm, which stain for mucin.

### Chapter 14

## Classification of Gestational Trophoblastic Disease

### 1) Benign:

- The benign form is called hydatidiform mole or molar pregnancy.
- Hydatidiform Mole is of two types, both type result from abnormal fertilization and in both types, elevation of hCG in maternal blood and absence of fetal heart sounds are typic

### Complete Mole

- It is defined as the abnormal pregnancy, which consists of placental tissue only, and there is no embryo in it.
- Macroscopically complete mole resembles a <u>Bunch of Grapes</u>.
- Karyotype: 46XX and rarely 46XY

#### \* Partial Mole:

- In this type of hydatidiform mole, the embryo or fetus co-exist with the placental abnormality.
- Karyotype: Triploid chromosome number: 69, XXY

#### 2) Malignant:

The malignant form is called Choriocarcinoma.

- 50% of Choriocarcinoma is arising from the complete hydatidiform mole.
- Lungs are the favorite site of Choriocarcinoma to metastasis, the characteristic radiological appearance of lung secondaries is called cannon-ball appearance.
- Occur during the period of pregnancy.

#### 3) Invasive mole:

- Invasive mole are complete mole that are <u>locally</u> aggressive but do not have the aggressive metastatic potential of Choriocarcinoma.
- Invasive mole is always proceeding by hydatidiform mole while the complete hydatidiform mole in 50% cases precedes Choriocarcinoma.
- On histology presence of villous structure indicate invasive mole while their absence represents Choriocarcinoma.



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### **Important Staging System**



### Staging system for uterine sarcoma

Stage	Description
Stage I	Sarcoma confined to the uterus
Stage II	Sarcoma involving the corpus and cervix
Stage III	Sarcoma spreading beyond the uterus, but not outside the pelvis
Stage IV	Sarcoma spreading outside the pelvis or into the bladder or rectum

Pathology & Physiology of Male & Female Genital System

# The FIGO staging of Vulvar cancer

- Contract	Definition
Stage	Confined to vulva and/or perineum, 2 cm or less maximum
Stage la	diameter. Groin nodes not palpable. Stromar invasion no greater
	As for la but stromal invasion is greater than 1 mm
Stage Ib	
Stage 2	Confined to vulva and/or perineum, more than 2 cm maximum diameter. Groin nodes not palpable
Stage 3	Extends beyond the vulva, vagina, lower urethra, or anus, or
Stage 4a	Involve the mucosa of rectum or bladder, upper urethra or pelvic bone and/or bilateral regional lymph node metastasis
Stage 4b	Any metastasis, including pelvic lymph nodes

### FIGO Staging for Vaginal cancer

Stage	Description	
Stage 0	Intraepithelial neoplasia	
Stage 1	Invasive carcinoma confined to vaginal mucosa	
Stage 2	Sub vaginal infiltration not extending to pelvic wall	
Stage 3	Extend to pelvic wall	
Stage 4a	Involve mucosa of bladder or rectum	
Stage 4b	Spread beyond the pelvis	

### FIGO surgicopathological staging of endometrial carcinoma

Stage	Definition	
Stage la	Tumor limited to endometrium	
Stage Ib	Invasion < half myometrium	
Stage Ic	Invasion > half myometrium	
Stage II	Endocervical glandular involvement only	
Stage IIb	Cervical stromal invasion	
Stage IIIa	Tumor invades serosal and/ or adnexal and/ or positive peritor cytology	
Stage IIIb	Vaginal metastasis	
Stage IIIc	* * - to stack to pelvic and/or para portion	
Stage Iva	Tumor invades bladder and/ or bowel mucosa	
Stage Iva	Distant metastasis including intra abdominal/ and/ or vaginal nodes	

### FIGO staging for Primary Ovarian Carcinoma

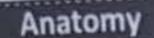
Stage	FIGO Definition	
Tr. Serie	Growth limited to ovaries	
a	Growth limited to one ovary, no Ascities, no tumor on external surface, capsule intact	
b	Growth limited to both ovary, no Ascities, no tumor on external surface, capsule intact	
C	Tumor either stage la or lb but tumor on surface of one or both ovaries, or with capsule ruptured or with ascites present containing malignant cells, or with positive peritoneal washings	
II	Growth involving one or both ovaries with pelvic extension	
Ila	Extension and/ or metastasis to the uterus or tubes	
llb	Extension to other pelvic tissues	
IIC	Tumor either stage IIa or IIb but tumor on surface of one or both ovaries, o	
<u>III</u>	Growth involving one or both ovaries with peritoneal Implants outside the pelvis or positive retroperitoneal or inguinal nodes. Superficial live metastasis equals stage III	
Illa	Tumor grossly limited to the true pelvis with negative nodes but with Histologically confirmed microscopic seeding of abdominal peritone surfaces.	
IIIb	Tumor with Histologically confirmed implants on abdominal peritone surface none exceeding 2 cm in diameter. Nodes are negative	
IIIc	Abdominal implants greater than 2 cm in diameter or positive retroperitoneal or inguinal nodes	
<u>IV</u>	Growth involving one or both ovaries with distant metastasis. If pleurs effusion is present, there must be positive cytology to allot a case to stage IV. Parenchymal liver metastasis equals stage IV	

## CHAPTER

# BREAST







### High-yield points:

- ✓ Specialized accessory gland of the skin that secretes milk
- ✓ Each breast consist of 15-20 lobes
- ✓ The breast is Modified sweat gland
- ✓ Fat deposition in the breast is due to estrogen
- ✓ Breast atrophy: The atrophy after menopause is caused by an absence of ovarian estrogens and progesterone. (reference: SNELL 8th edition P.427)

### Deep relation of the breast:

- ✓ The breast lies on the deep fascia (pectoral fascia) covering the pectoralis major muscle.
- Still deeper there are four muscles, namely, pectoralis major, Serratus anterior, latissimus dorsi and external oblique muscle
- Breast is separated from pectoralis fascia by loose Areolar tissue (Retromammary space)
- Because of this loose tissue, the normal breast can be moved freely over the pectorals major
- ✓ Surgical importance: During removal of breast, the breast is separated from pectorals muscle in plane of Retromammary space
- ✓ During radical mastectomy, the nerve supply to Serratus anterior and latissimus dors of preserved

### % Structures:

✓ Areola: Epithelium of areola contains numerous modified sweat glands and the sebaceout glands. These gland enlarge during pregnancy (gland of Montogomery)

### The Architecture of parenchyma:

- ✓ Parenchyma consist of 10-100 lobules
- ✓ Each lobule is a cluster of alveoli drained by a lactiferous duct, which near its termination dilate to form lactiferous sinus
  - 1. Carcinoma within breast the breast substances can cause retraction of nipple due pulling on lactiferous duct

### % The stroma:

- ✓ It forms the supporting framework of the breast. It is partially fibrous and partly fatty
- Fibrous part: "ligament of Cooper" hollow conical projection of fibrous tissue filled will breast tissue. It anchors the skin and gland to the pectoral fascia
- Fatty stroma forms the main bulk of the gland. It is distributed all over the breast, ext

### Chapter 15

Breast

beneath areola and nipple.

✓ Amount of adipose tissue determine the size of the breast

### Embryology:

- ✓ The epithelial lining of the ducts and acini of the breast develops from ectoderm.
- ✓ The supporting tissue develops from mesenchyme

### & Extent:

- ✓ Vertically: it extends from 2<sup>nd</sup> to 6<sup>th</sup> rib
- ✓ Horizontally: it extends from the lateral border of the sternum to the mid-axillary line.

### & Blood supply:

- ✓ Perforating branches of the internal thoracic artery (branch of the subclavian artery)
- √ Intercostal artery
- √ Axillary artery

### & Venous drainage:

✓ The vein corresponds to the arteries

### & Lymph drainage:

- ✓ Anterior axillary or pectoral group:
  - About 75% drain into the pectoral group
  - Drain lateral, nipple and superior part of the breast
  - o The pectoral nodes receive lymph mainly from the anterior thoracic wall, including most of the breast
- ✓ Internal thoracic group of node: 20%
  - Drain medial quadrant of the breast
- ✓ Posterior intercostal node: 5%.
- ✓ Some communicate with the opposite breast and with those of the anterior abdominal wall

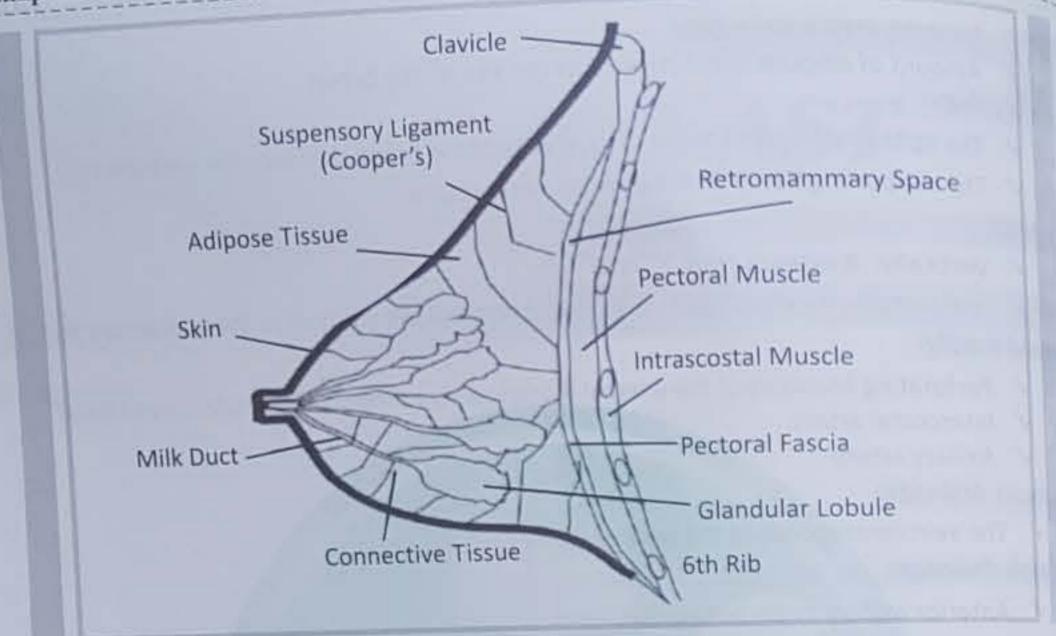
### % Some terms:

- ✓ Lymphangitis----inflammation of lymph vessels
- ✓ Lymphadenitis----inflammation of lymph nodes
- ✓ Lymphoedema----obstruction to lymph vessels leading to edema, the incidence of functionally significant lymphoedema after a modified radical mastoidectomy is approximately 20% but can be as high as 50% to 60% when postoperative radiation is employed

### & Gynecomastia:

Breast enlargement in males due to increase estrogen compared with androgen activity

- ✓ Drug causing Gynecomastia:
  - o Griseofulvin -----antifungal
  - o Spironolactone
  - o Cimetidine o Ketoconazole
- ✓ The Drug not causing Gynecomastia:
  - o Androgen



### Physiology of Breast

- Estrogens-----Develop the duct system and cause fat deposition in breasts.
- Progesterone-----Develop the milk-secreting glands, which are called alveoli
- Three hormones are responsible for milk production PCO: Prolactin, Cortisol and Oxytocin
- Prolactin-----Stimulate milk synthesis in the alveoli
- -Stimulate milk ejection from the alveoli Oxytocin-
- --- have an important lactation inducing function

#### Lactation

- Lactation doesn't occur in pregnancy because----estrogen and progestin block the action is Prolactin on breast
- Amenorrhea in lactation is due to----inhibition of LH and FSH through Prolactin
- Ovulation is inhibited In lactation by Prolactin which causes:
  - ✓ Inhibit hypothalamus GnRH secretion
  - ✓ Inhibit GnRH action on anterior pituitary, and consequently inhibit LH and FSH
  - ✓ Antagonize the action of LH and FSH on ovaries
- Lactation is maintained by-----suckling, which stimulate oxytocin and prolactin
- Prolactin release from anterior pituitary gland inhibited by Bromocriptine

- Women with a positive family history of breast cancer are in a higher risk of developing breast cancer and the most common gene mutation associated with developing breast cancer is BRCA -1 and BRCA-2 gene mutation.
- 2) Mammography is the gold standard test for breast cancer
- 3) The Commonest site for breast carcinoma is the upper outer quadrant of the breast.
- 4) Breast cancer is the most common cancer during pregnancy
- 5) Pleomorphic calcification is the hallmark of Ductal carcinoma in Situ (DCIS), which is typically found on mammographic examination.
- Coarse calcifications are usually benign. Fine, clustered calcification are often malignant and require biopsy.
- 7) LCIS is often multifocal and bilateral. It discovered incidentally.
- 8) Fibroadenoma is also known as "Breast Mouse" because of its mobility and is the most common benign tumor of the female breast younger than 25 years of age. Fibroadenoma are partially hormone dependant and frequently regress after menopause.
- 9) The most common cause of bloody discharge from the nipple is intraductal papilloma. The lesion is treated by excision and is benign in most cases. Cancer is present in 5% of cases
- 10) Invasive or infiltrating ductal carcinoma is the most common variant of breast carcinoma (around 80%). Worst and most invasive. Classic "satellite" morphology.
- 11) Peau d'orange: it is an orange-colored appearance of skin caused by cutaneous lymphatic edema & important clinical feature of inflammatory breast carcinoma.
- 12) Inflammatory breast cancer is a very aggressive form of breast cancer characterized by Intradermal lymphatic spread of tumor
- 13) Paget disease of the nipple: it is a superficial manifestation of an underlying breast carcinoma. It is a malignant condition resulting in the eczematoid change of the nipple caused by:
  - i. Ductal carcinoma in situ (DCIS) OR
  - ii. Invasive breast cancer growing along the duct onto the nipple surface
- 14) "Sentinel Nodes" are small group of nodes that are the first to receive the lymphatics. Sentinel node biopsy is currently the mainstay for staging the axilla.
- 15) Premalignant intra-epithelial lesion of the vulva is also called Paget diseases of the vulva
- 16) Fat necrosis is a lump of dead or damaged breast tissue that sometimes appears after breast surgery, radiation, or another trauma.

### Chapter 15

# Risk factor for Breast Carcinoma: RPN FOOD HAL

- R-----Race and ethnicity
- P previous irradiation history
- N------Nulliparity
- F------Family history
- O-----Obesity
- O-----Oral contraceptive pills
- D------Diet low in phytoestrogen
- H------Hormonal replacement therapy, High alcohol consumption
- A------Aging
- L -----lack of breast-feeding

#### & Genetic risk:

- ✓ BRCA 1 and BRCA 2 mutation—chromosome 13 and 17 contain the two known tumor suppressor gene, BRCA2 at 13 and BRCA1 at 17. BRCA 1 mutation patient are 55% more likely to get ovarian cancer
- √ Ataxia telangiectasia
- ✓ Cowden Syndrome

#### Name of receptor in breast

- Estrogen receptor
- Progesterone receptor
- "HER2/NEU" receptor: ——Patients with HER2/neu positive breast tumor are more aggressive and have a worse prognosis compared to HER2/neu negative tumors. Trastuzumab is a monoclonal antibody against HER2/neu and is indicated for patients with breast cancer the overexpress HER2/neu

### Classification of Breast Carcinoma

Breast cancers are divided into those that have not penetrated the basement membrane (noninvasive) and those that have (invasive)

### i. Non -invasive

- Ductal carcinoma in situ (DCIS)
- · Lobular carcinoma in situ (LCIS)

#### ii. Invasive

- . Invasive or infiltrating ductal carcinoma more than 80% (imp)
- Invasive lobular carcinoma 15%
- Medullary carcinoma
- Colloid carcinoma
- Inflammatory carcinoma
- · Paget's disease of the nipple

### Chapter 15

### Important Prognostic Factor in Breast Carcinoma

### 1

Breast

### A. Axillary lymph node Metastasis:

- . It is the single best marker for prognosis
- \* If positive, the prognosis is poor
- The number of positive axillary nodes remains one of the best prognostic indicators in breast carcinoma

#### B. Tumor size:

- It is the second most important prognostic factor
- If >2cm prognosis is poor

#### C. Distant metastasis:

. If present cure is unlikely

### D. Estrogen and progesterone receptor

- · Receptor positive tumor respond to hormone therapy
- Receptor positive tumor, therefore, have better prognosis.

#### Breast Implant

- A breast implant is a prosthesis used to change the size, shape and contour of a women's breast.
   In reconstructive plastic surgery, the breast implant can be placed to restore a natural looking breast mound for post-mastectomy breast reconstruction patient or to correct congenital defect and deformities of chest wall
- When breast implant removed and there is leaking of fluid <u>OR</u> When breast implant not removed
  and there is leaking of fluid and there are no sign of inflammation the type of cell which will be
  present are <u>Giant cell</u>
- When Implant removed or not removed or whether leaking present or absent but there are the sign of inflammation like tenderness the type of cell which will be present are neutrophils
- But Silicones breast implant produces foreign body giant cell and chronic inflammation---no neutrophil in silicones breast implant
- In simple words in breast implant type of cells are Giant cells but when inflammation mentioned then neutrophils. So only two types of cell are present in breast implant (giant cell and neutrophil) and there is no role of immunity so there will be no plasma cell

spine which have been proved the party

# CHAPTER

HEMATOLOGY

"Of all that is written, I love only what a person has written with his own blood"\_\_Friedrich Nietzsche

# PHYSIOLOGY

**Blood Products** 

### Warfarin toxicity treatment

- Acute-----FFP
- Chronic-----Vit-K

### Cryoprecipitate for the following deficiency

- Factor eight and 13, when no specific factor 8 concentrate available, the next best source of factor 8 is cryoprecipitate
- VWF
- Fibrinogen

#### Washed RBC:

Transfusing washed RBC components usually prevent Allergic or hypersensitivity reaction

### Whole blood for 3 days:

NAME AND ADDRESS OF THE OWNER, WHEN

Soldier with heavy bleeding

### Fresh Frozen Plasma (FFP) for:

- Factor 9 deficiency
- Acute warfarin toxicity
- In severe liver disease to combat the bleeding disorder
- Transfusions with FFP to replenish Vitamin-K dependent clotting factor should be administered on call to the operation room. The half-life of the most stable clotting factor Factor VII is 4 to 6 hours. Thus, the transfusion of FFP on call to the operating room ensures that the transfusion is complete prior to the incision, with circulating factors li cover the operative and immediate postoperative period

### Storage of Blood Products

- Whole blood is stored at 4°C for 3 weeks
- Packed cells (RBCs) are stored at 1-6° for 35 days
- FFP and cryoprecipitate can be stored at -40 °C for 2 years
- Platelets are stored at 22°C for 5 days
- · Platelets are given at room temperature to optimize their function

### Stored blood:

- The first factor lost from stored blood is 2-3 DPG due to decrease in Ph, lead to increase in oxygen affinity. Stored blood is deficient of factor 5 and 8
- Hemolysis occurs which results in raised plasma Hb

#### **Key Differences**

- serum: If whole blood is allowed to clot and the clot is removed remaining fluid is called serum or plasma minus factor 2,5,8 and fibrinogen is called serum-----Serum = plasma -clotting factors
- Plasma: Plasma is that part of ECF, which is identical to interstitial fluid, but contains 7% proteins, while interstitial fluid contains 2% protein. All plasma protein is formed in the liver except, Gamma globulin, which is formed in Reticuloendothelial cell, plasma cell and lymphocytes. Albumin is the most common plasma protein. Factor VII is present both in plasma and serum
- \* Buffy coat----The fraction of an anticoagulant blood sample that contains most of the white blood (WBC) and platelet
- . Hematocrit: The proportion of the blood that is red blood cell is called the hematocrit. Normal value is 40-45%, newborn: up to 60%
  - Low hematocrit------Anemia, pregnancy
  - High hematocrit------High altitude, chronic smoker, lung disease, tumors

### Red Blood Cell (RBCs)

- Most numerous of the formed elements of the blood is RBC
- RBCs are anucleate and biconcave cells that stain light salmon pink with either Wright or Giemsa stains
- Have the glycolytic pathway
- In RBC there is an alternate pathway of Glycolysis resulting in the formation of 2,3-BPG
- \* RBC destroyed in the spleen
- Normal RBCs have a diameter of 6 8 μm—average 7.5 μm
- ABO blood group are glycoprotein attach to RBC surface
- \* RBC antigen are glycoprotein and are secreted in Saliva
- . The Cell which uses glucose is RBC and organ which use glucose for energy is the brain
- \* The Shape of RBC is maintained by Spectrin
- For Arterial-Blood Gas (ABG), whole blood is heparinized. Most common site for obtaining ABG is radial artery
- The function of RBC is to carry gases
- Difference between arterial blood and venous blood is packed cell volume.
- Size of RBC is greater in veins than arteries
- 2 weeks of blood will contain only RBC
- The life span of RBC is 120 days, the life span of RBC in the neonate is 70-90 days
- Old RBC are removed in capillaries and red pulp
- \* RBC breakdown will result in the release of iron which can be reutilized
- \* RBC able to regenerate due to erythropoietin
- \* Blood cell able to regenerate due to growth factor
- Total circulating blood is 8% of total body weight
- Blood is not a major basic tissue
- \* Hypoxia is the stimulation for production of erythropoietin
- Blood is the least irritating substance when free in the peritoneal cavity
- The Brain can use ketone instead of glucose in starvation while RBC cant utilize ketone, they strictly use glucose

Hematology

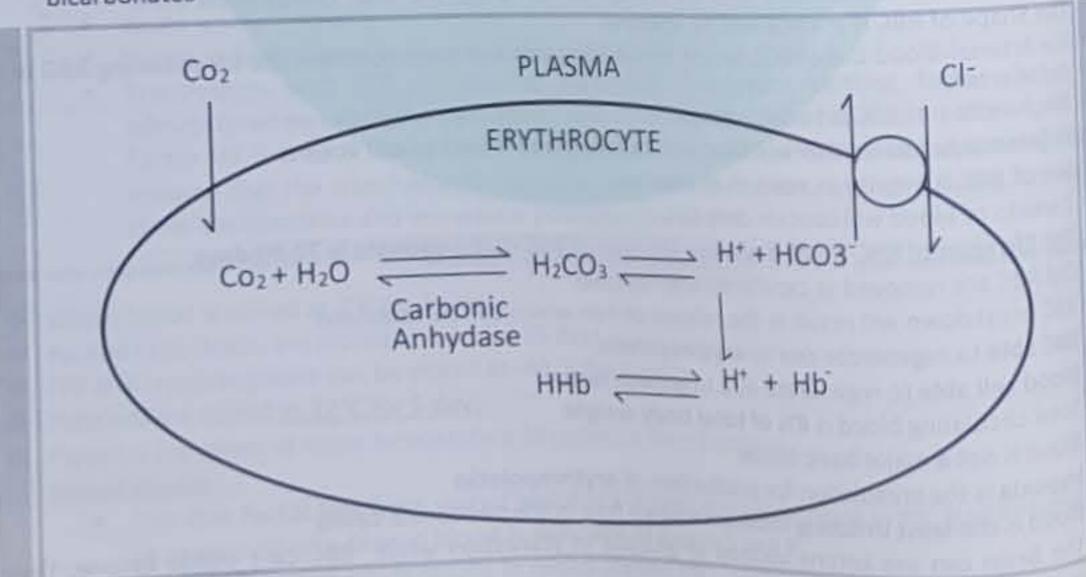
NAME AND POST OFFICE ADDRESS OF THE OWNER.

# The Fate of Carbon Dioxide in Blood

- The solubility of CO<sub>2</sub> in blood is about 20 times that of O<sub>2</sub>; therefore, considerably more CO<sub>2</sub> than O<sub>2</sub> is present in simple solution at equal partial pressures.
- The CO₂ that diffuses into red blood cells is rapidly hydrated to H₂CO₃ because of the presence of the presence of the presence of the CO₂ that diffuses into red blood cells is rapidly hydrated to H₂CO₃ because of the presence of carbonic anhydrase. The H<sub>2</sub>CO<sub>3</sub> dissociates to H<sup>+</sup> and HCO<sub>3</sub>, and the H<sup>+</sup> is buffered, primarily by hemoglobin, while the HCO<sub>3</sub> enters the plasma. Some of the CO<sub>2</sub> in the red cells reacts with the amino groups of hemoglobin and other proteins (R), forming carbamino compounds. About 11k of the CO2 added to the blood in the systemic capillaries is carried to the lungs as carbamino-CO3
- The amount of CO<sub>2</sub> dissolved in the fluid of the blood at 45 mm Hg is about 2.7ml/d (2.7 volume percent)

### Chloride Shift

- ❖ Because the rise in the HCO₃ contents of red cells is much greater than that in plasma as the blood passes through the capillaries, about 70% of the HCO3 formed in the red cells enters the plasma. The excess HCO3 leaves the red cells in exchange for CIT. This process is mediated by anion exchanger 1 (AE1; formerly called Band 3), a major membrane protein in the red blood cell. Because of this chloride shift, the CF content of the red cells in venous blood is significantly greater than that in arterial blood. The chloride shift occurs rapidly and is essentially complete within 1 s.
- \* Note that for each CO2 molecule added to a red cell, there is an increase of one osmotically active particle in the cell—either an HCO3 or a Cl in the red cell. Consequently, the red cells take up water and increase in size. For this reason, plus the fact that a small amount of fluid in the arterial blood returns via the lymphatics rather than the veins, the hematocrit of venous bloods normally 3% greater than that of the arterial blood. In the lungs, the CIT moves out of the cells and they shrink.
- ❖ Venous blood have more HCO₃, 90% of CO₂ is primarily transported in the arterial blood asa bicarbonates



# Chapter 16

#### **Blood Volume**

- Physiological variation
- . Age:
  - ✓ In the infant blood volume is greater in proportion to body weight, but lesser in proportion to body surface
- . Sex:
  - ✓ In male, the blood volume is greater than female due to greater RBC count
- · Pregnancy:
  - ✓ Blood volume increase due to increase in cells and plasma
- Exercise
  - ✓ Blood volume increase due to muscle and spleen contraction
- Posture:
  - ✓ In erect posture blood volume decrease because plasma passes out into tissue spaces
- Blood pressure:
  - ✓ Increase BP decrease blood volume by shifting more fluid into tissues.
- · Altitude:
  - ✓ Increase altitude increase blood volume due to hypoxia that increase RBC count
- \* Physique:
  - Blood volume is less in obese because adipose tissue has less H2O
- ❖ Blood volume: Shock manifest at about 25% blood loss
  - ✓ Preterm: 100-120ml/kg
  - ✓ Neonate: 80-90 ml/kg---example 5kg neonate = 5 X 85 (average) = 420ml blood
  - ✓ Infant: 85ml/kg
  - √ Child: 80 ml/kg
  - ✓ Adult: 70ml/kg

### Site of Erythropoiesis

### Intrauterine:

- Early few weeks------Yolk sac (nucleated RBC)
- Middle trimester-----liver mainly
- Last month and after birth: exclusively in bone marrow.

#### After birth:

- Until 5 years-----All bone marrow
- 5-20 years——Bone marrow of long bone become yellow(except proximal humeri and tibia)
- \* After 20 years--in the marrow of membranous bone e.g. vertebra, sternum and ileum
- No Erythropoiesis occurs in kidney

## Stages of Erythropoiesis: PB-PORE



### Pro-erythroblast:

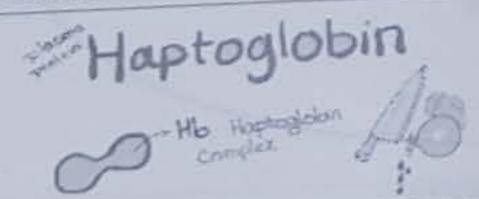
- Hb synthesis begins in this stage
- Reasophile erythroblast/Early Normoblast:
  - Very little Hb
  - Nucleoli disappear
- Poly-Chromophil erythroblast/Intermediate Normoblast

- Hb starts appearing, Enough Hb present
- Polychromasia: red cell stain shades of blue-gray as a consequence of uptake of book Polychromasia: red cell stall and basic dyes (by residual ribosomal RNA). Found in bleeding hemolysis or response to haemostatic factor replacement
- Orthochromatic erythroblast/Late Normoblast
  - The maximum or very large amount of Hb production occurs in this stage
  - Nucleus disappear
- Reticulocyte:
  - Maximum Hb concentration present
  - Reticulum is formed
  - Normal 1-2%
- Mature RBC:
  - Cell attain biconcavity

### Hemoglobin

- Hb is a conjugated protein made of Heme and globin
- . Heme is converted into Bilirubin mainly in the spleen
- Heme consist of porphyrin and iron, Hb contains 70% of iron
- \* Each Hb molecule can bind 4 oxygen molecule
- 1 hemoglobin molecule transports 8 atoms of oxygen
- . Each iron atom binds to 1 oxygen molecule
- . Hb molecule has 4 atoms of iron
- RBC can concentrate Hb up to 34mg/100ml
- ❖ Each gm of Hb can bind 1.34ml of 02, 10gm Hb will contain 13.4 ml (10 x 1.34 = 13.4)
- \* Half-life of carboxyhemoglobin in room air is 4-6 hours
- A physiologic decrease in hemoglobin content is noticed at 8-12 weeks in term infant (hemoglobin, 11 g/dl) and approximately 6 weeks in premature infants (7-10 gm/dl). Therefore Hb is least in newborn when at the age of 3 months.
- The hemoglobin oxygen saturation of blood entering the right ventricle is approximately 75%

#### Haptoglobin In intravascular hemolysis, free hemoglobin will circulation into released hence haptoglobin will bind the hemoglobin. This causes a decline in haptoglobin levels. The half-life of haptoglobin is 5 days



### Hemopexin

Hemopexin is the plasma protein with highest binding affinity to heme among known proteins. It is mainly expressed in liver, and belongs to acute phase reactants, the synthesis of which is induced after inflammation.

When Hemoglobin binds with haptoglobin and

Heme binds with hemopexin, they retained in the vasculature, diminishing tissue damage

#### Chapter 16

Hematology

### Normal Human Hemoglobin

- b Embryonic Hb: Red cells appearing first at about 6 weeks after conception contain the embryonic hemoglobin
  - ✓ Gower I Hb: 2 zeta ( $\zeta_2$ ) + 2 epsilon ( $\epsilon$ 2), during the period of yolk sac hematopoiesis the earliest hemoglobin called the grower Hb I
  - ✓ Gower II Hb: 2 alpha + 2 epsilon
  - ✓ Portland Hb: ζ₂γ₂
- Fetal hemoglobin: HbF
  - 2Alpha + 2 Gamma: it has the Least affinity for 2,3-BPG and has a higher affinity for O₂ than adult Hb. Appear in the period of liver hematopoiesis
  - At 12-11 weeks, fetal hemoglobin becomes predominant, switch to nearly exclusive of adult hemoglobin occur at about 38 weeks
- Adult Hemoglobin:
  - ✓ HbA-----2 Alpha + 2 Beta----Normal Hb, 97%
  - √ HbA₂-----2 Alpha + 2 Delta----1.5-3.2%
- Normal values:
  - ✓ Male Hb-----16gm/100ml
  - √ Female Hb----14gm/100ml

#### Abnormal Hb

- NAME AND POST OFFICE ADDRESS OF THE OWNER, WHEN PERSON NAMED IN COLUMN 2 IS NOT THE OWNER, WHEN PERSON NAMED IN COLUMN 2 IS NOT THE OWNER. HB-S------Glutamic acid replaced by Valine at position no 6 in beta chain, undergo sickling at low 02 tension
- Hb-C-----Glutamic acid replaced by lysine at position No.6 in beta-chain
- Hb-E-----Glutamic acid replaced by lysine at position No.26 in beta-chain
- Hb-M (Methemoglobin) ------Contain iron in ferric iron (Fe<sup>3+</sup>) form rather than ferrous iron (Fe<sup>2+</sup>).

### Derivatives of Hb

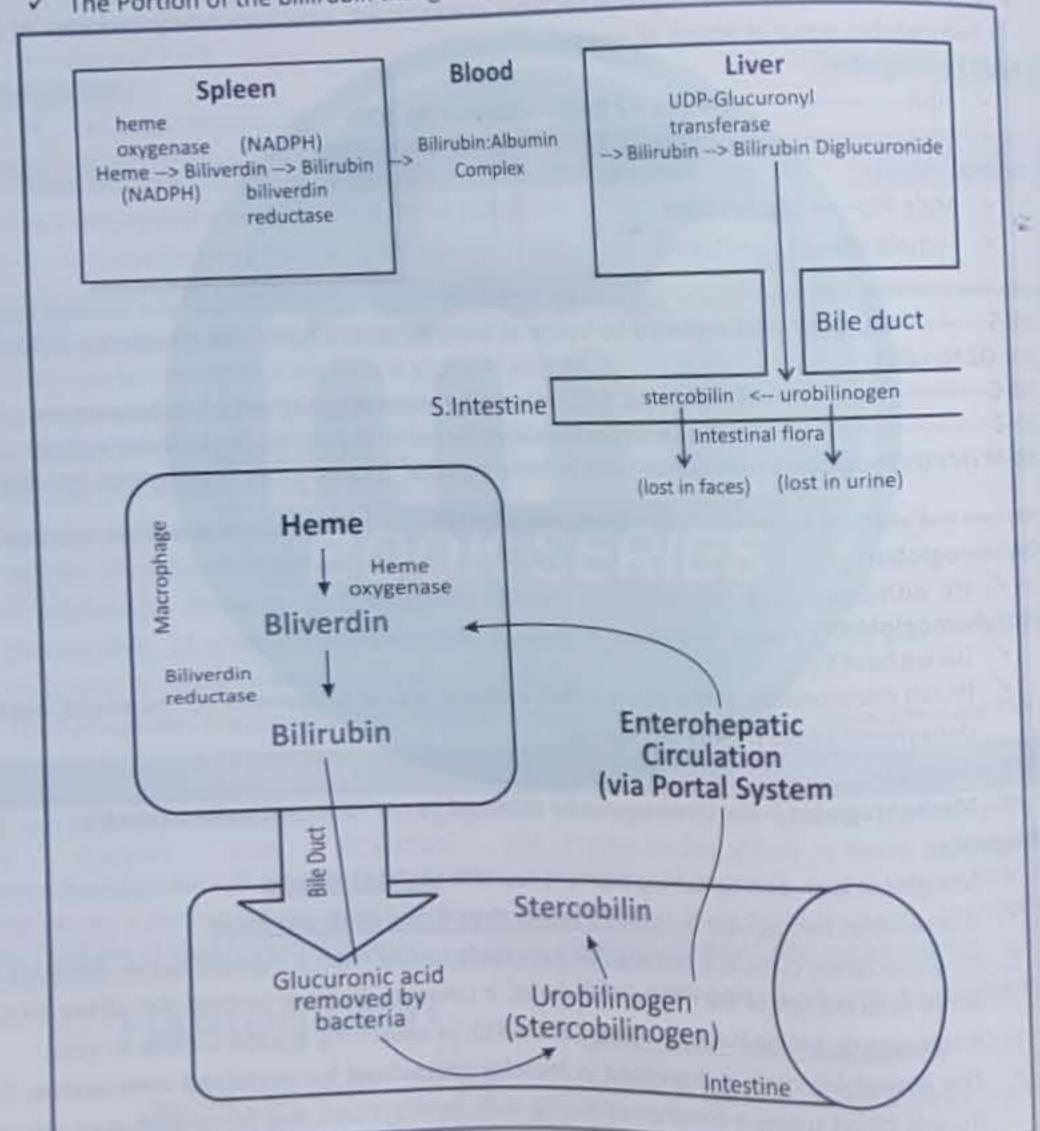
- Oxyhemoglobin:
  - ✓ Hb with 0<sub>2</sub>
- Deoxyhemoglobin:

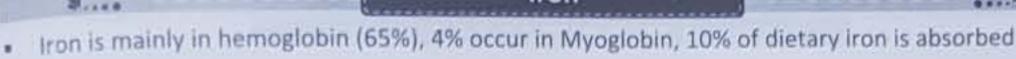
  - ✓ Hb without 0₂ Bluish discoloration of the skin is called cyanosis, Cause of cyanosis is, increased level of deoxyhemoglobin (more than 5gm/dl)
- \* Methemoglobin:
  - Methemoglobin in the blood cannot be detected by conventional pulse oximetry.
- Myoglobin:
  - ✓ Myoglobin is an iron-containing pigment found in <u>skeletal muscle</u>.
  - ✓ It resembles hemoglobin but binds 1 rather than 4 mol of O₂ per mole.
  - ✓ Its dissociation curve is a rectangular hyperbola rather than a sigmoid curve. Because its curve is to the left of the hemoglobin curve, it takes up O2 from hemoglobin in the blood. It releases O2 only at low PO2 values, but the PO2 in exercising muscle is close to zero.
  - ✓ The Myoglobin content is greatest in muscles specialized for sustained contraction. The muscle blood supply is compressed during such contractions, and Myoglobin may provide O2 when blood flow is cut off. Page | 407

Hematology

### Formation of Hb

- Site: Most steps occur in mitochondria
- Steps:
  - Acetic acid → Succinyl CoA
  - 2 succinyl CoA + 2 Glycine → Pyrrole
  - ✓ 4 pyrrole → protoporphyrin IX
  - Protoporphyrin IX + Fe++ → Heme
  - ✓ Heme + globin → Hemoglobin
  - ✓ 2 alpha-chain + 2 beta-chains → Hb molecule (Hb A)
  - ✓ The Portion of the billirubin that gives pale color to feces is stercobilin





- Iron stored in female-----2.4gm
- Iron stored in males----------4 gram
- · Iron bind with Hb

Chapter 16

- Iron stored in parenchymal tissue in the soluble form—ferritin
- Insoluble form of iron-----hemosiderin
- The main regulator of Iron absorption-------Hepcidin = A protein formed by the liver
- The daily loss of iron: In male =1mg (into feces), Female: 2mg (into feces and menstrual blood)
- Iron tablet taken on an empty stomach which helps the body absorb them better
- The best indicator of serum iron store is serum iron ferritin
- Iron demand in pregnancy: 800mg

AND REAL PROPERTY AND REAL PRO

- Approximately 70% of body iron is found bound to hemoglobin
- Ferrous fumarate has approximately 33% elemental iron. Ferrous sulfate has 20% elemental iron. Ferrous gluconate has 12% elemental iron.

### Iron Deficiency Anemia

- Iron deficiency anemia is hypochromic Microcytic anemia
- Most common overall anemia, most common nutritional deficiency worldwide.
- Phytates, Tannates, phosphate, oxalate and carbonate all these have negative influence on iron
- Vitamin-C, citrate and glucose help to convert ferric iron (Fe<sup>3+</sup>) to ferrous iron (Fe<sup>2+</sup>), this Reduced (Fe2+), directly reabsorbed in the duodenum.
- Intestinal absorption of iron mainly occurs in ferrous form, which found most abundant in meat.
- Plant contains the ferric form of iron.

PRINCIPAL DESIGNATION AND ADDRESS OF THE PARTY NAMED IN COLUMN TWO IS NOT THE PARTY NAMED IN COLUMN TWO IS NAMED IN COLUMN TWO

- HbM bind with the ferric form of iron
- Iron stored in form of ferritin and transported in form of transferrin
- This is the most common cause of anemia in pregnancy

### Iron Poisoning

- One of the leading causes of fatality from toxicologic agent in children
- Mechanism: cell death due to peroxidation of membrane lipids
- Symptoms
  - -Gastric bleeding ✓ Acute----
  - -Metabolic acidosis, scarring leading to GI obstruction ✓ Chronic----

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# Erythrocyte Sedimentation Rate (ESR)

- In presence of an anticoagulant rate of settling-down of RBCs in the specimen of blood which is allowed to stand in a glass tube of the uniform bore, is called ESR
- RBCs settle down because they are heavier than plasma. ESR is enhanced by Rouleaux formation
- Increasing factors:
  - √ Increase O₂
  - ✓ Increase alpha-globulin
  - √ Increase cholesterol
  - ✓ Increase fibrinogen, because it favors Rouleaux formation
  - ✓ More than 100 in multiple myeloma
  - ✓ Acute infection due to proteins that enter plasma from site of the infection
- Decreasing factors
  - √ Increase CO₂
  - √ Increase lecithin
  - √ Increase albumin
  - √ Increase nucleoprotein
- Physiological variation:
  - ✓ Lowest in newborn
  - ✓ Increase in pregnancy after 3 months due to fibrinogen formation
  - ✓ Increase in old age

#### **Lead Poisoning**

- Severe lead poisoning is treated with succimer
- Diagnostic test: lead level In blood and urine
- Lead poisoning cause ALA synthase deficiency
- ABCDEF:
  - -----Anemia(Microcytic)/Amenorrhea
  - -Basophilic stippling of RBCs/Burtonian lines
  - -- Colic/Constipation
  - -Drop (wrist/foot)
  - -Encephalopathy
  - ----Facial pallor

#### Erythropoietin

- It is secreted by interstitial cell of kidney
- Strongest stimulus for release of erythropoietin is: Hypoxia (decrease in PO.)
- MOA of erythropoietin: Bind to specific EPO receptors (JAK-STAT-Kinase)
- Decreased erythropoletin level are seen in end-stage renal disease

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0011

Hematology

### **PATHOLOGY**

### **Pathognomonic Points**

DISEASE	HIGH YIELD
Paroxysmal Nocturnal Hemoglobinuria	Red urine in the morning
Methemoglobinemia	Chocolate color blood
Infectious Mononucleosis	Atypical cells
> Nodular sclerosis	Lacunars cell
Follicular lymphoma	Buttock cell
> Burkett's lymphoma	Starry sky, EBV is causative agent
> Thalassemia and myelofibrosis	Tear-drop cell

### **Investigation of Choice**

s/NO	DISEASE	INVESTIGATION OF CHOICE
T.	Folate Deficiency Anemia	RBC folate is the best indicator of folate store
ii.	Vitamin B-12 deficiency anemia	Increase in urinary methylmalonic acid
iii.	Deficiency of Vitamin B—12 in infant	Serum vitamin B12 level
iv.	Iron Deficiency Anemia	Decrease Serum Ferritin Level
٧.	Sickle Cell Anemia	Hb-Electrophoresis
vi.	Thalassemia	Hb-Electrophoresis
vii.	G6PD Deficiency Anemia	G6PD Level
viii.	PNH	Peripheral Blood Flow Cytometry
	Hereditary Spherocytosis	Osmotic Fragility Test
ix.		Decreased haptoglobin
х.	Hemolytic Anemia	Trephine Bone marrow biopsy
xi.	Aplastic Anemia	
xii.	Pyruvate Kinase Disease	RBC Enzyme Assay
xiii.	Pernicious Anemia	Antibody Against Intrinsic Factor

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# Classification of anemia on the bases of MCV

This is a very important way to learn anemia and diagnose anemia

Microcytic: MCV less than 80

Normocytic: MCV is equal to 80-100

Macrocytic: MCV greater than 100

What Is MCV and MCH?

✓ Mean corpuscular volume (MCV): it is the average volume of red blood cell

✓ Mean corpuscular Hemoglobin (MCH) Normal value=27-33pg: it refers to the average man of Hb per RBC.

✓ These tell us of Normo-chromic, Hypo-chromic or Hyper-chromic anemia

### This is how to differentiate L

- Iron deficiency anemia: Low iron, Low ferritin, and High TIBC---everything is low except TIBC which is high
- Anemia of chronic disease: Low iron, High ferritin and Low TIBC---everything is low except ferritin which is high
- Hemochromatosis: High ferritin, High iron, High percent saturation, Low TIBC---- everything is high except TIBC which is low.

### Various Important site for absorption

Mnemonic: Dude Is----just feeling----ill Bro

- -Duodenum Absorption of iron:---
- Absorption of folate:---Jejunum
- Absorption of B12:---Terminal ileum

### Microcytic Anemia etiology MCV< 80fl (Mnemonic TAILS)

- -Thalassemia
- -Anemia of Chronic disease
- -Iron deficiency anemia
- -Lead poisoning
- -Sideroblastic anemia—(iron-laden mitochondria)

### Aplastic anemia

#### a Causes:

- Idiopathic-most common causes
- Inherited -- Fanconi anemia
- Drugs-most common know cause (benzene, Chloramphenicol, alkylating agent # Antimetabolites)
- Radiation

### Chapter 16

Hematology

- Viral agent (parvovirus B-19), EBV, HIV, HCV)
- Splenomegaly is characteristically absent.
- CBC: Pancytopenia
- Bone Marrow finding:
  - It is the most accurate method
  - Normal cell morphology
  - Hypocellular bone marrow with fatty infiltrate
  - Dry bone marrow tap

#### & Treatment:

- Young patient (<30)------Allogeneic bone marrow transplantation is curative
- Old patient: immunosuppressive therapy with cyclosporine and anti-thymocyte globulin

### **Hereditary Spherocytosis**

- It is an autosomal dominant disease, a structural defect in RBC
- Increase MCHC only occurs in hereditary spherocytosis that is why it is also called Normocytic hyperchromic anemia.
- Splenomegaly is most common and prominent in hereditary spherocytosis (HS) than any other form of hemolytic anemia that's why splenectomy is curative in hereditary spherocytosis.
- The most commonly employed test for hereditary spherocytosis is osmotic fragility test
- In osmotic fragility test, red blood cell swells/destroyed or ruptured in hypotonic solution (0.45% NaCl) and shrink in hypertonic solution, Red blood cell swell when placed in urea 250mmol
- Hereditary spherocytosis is accompanied by increased incidence of Cholelithiasis

### Sickle cell disease



- · Point mutation at position 6 of beta-globin chain of hemoglobin which is a protein
- . Heterozygous condition, which is also called sickle cell trait i-e Hbs contain, two population of RBC, 60% normal and 40% is sickle Hb (hbs). This is protective against falciparum malaria and produces no anemia.
- \* Homozygous condition, which is also called sickle cell anemia i-e Hbss. It contains 100% Hbs with no normal cell. This is not protective against falciparum malaria
- Hb-F protects us from sickling in sickle cell anemia.
- Sickling is precipitated by Hypoxia, Infection, Dehydration and Acidosis (mnemonic HIDA).
- The Vaso-occlusive crisis is the most common crisis in sickle cell anemia, which cause hand and foot syndrome (Dactylitis), and acute chest syndrome (which is the most common cause of death in adults)
- \* The Clinical finding of sickle cell anemia is susceptibility to infection like oste0myelitis, meningitis and sepsis, three kinds of crises like Vaso-occlusive crisis, aplastic crises (due to parvovirus B-19) and sequestration crises. Page | 413

#### Thalassemia DI MOHSIA

ssemia is due to gene deletions

oha Thalassemia:

rrier: Deletion of one alpha chain alassemia trait: Deletion of two alpha chain

ease: Deletion of three alpha chain

fetalis: Deletion of all four alpha chain, it is the most

atible with life

ia is due to point mutation in the splice site and promoter s ia minor (heterozygous):

in is underproduced

asymptomatic,

rophoresis show decrease HbA, normal HbF and raised HbA nia major (homozygous):

nin absent, severe anemia

alassemia major is also called Cooley's anemia

trophoresis show absent HbA, markedly raised HbF and H

alassemia major cause severe Microcytic anemia and pat

#### ion due to which there is an increased risk of Iron overload Megaloblastic Anemia

tosis: deficiency

ency ic drugs (methotrexate)

ism

syndrome

lost in Gastrectomy leads to the deficiency of intrinsic factor

tation----"Lemon-Yellow" skin and "Beefy" Red tongue

in balance europathy

sis of Megaloblastic anemia:

Hematology

Hematology

#### Polycythemia Vera

- Clinical features
  - ✓ Itching after a hot shower with dizziness & splenomegaly are characteristic features of Polycythemia Vera.
  - ✓ Headache and visual problem
- Polycythemia Vera is associated with JAk2 kinase mutation.
- Increase in blood concentration
- The decrease in EPO and lymphocyte level
- Increase in basophile cell
- Cobalt (half-life 5 years) can cause Polycythemia Vera
- There is an increase in Cardiac Output
- Platelet count may be raised
- Secondary Polycythemia:
  - ✓ EPO increase in secondary Polycythemia, increase EPO level is also seen in renal cell carcinoma
  - √ Packed cell volume (PCV) > 40

#### G6PD Deficiency—Genetic disorder

- G6PD is inherited is an X-linked recessive manner and symptoms are more common in males
- Most common enzyme related hemolytic anemia
- Bite-cell: Bite-cell are erythrocyte with the bite of cytoplasm being removed by the splenic macrophage.
- Heinz body: Which form from denatured hemoglobin
- Mostly drug-induced and self-limiting and Spleen size is normal
- All individual with favism (hemolytic response to the use of broad beans) show G6PD deficiency

#### Autoimmune Hemolytic Anemia (AHA)

- The most common cause of primary AHA is idiopathic
- Autoimmune hemolytic anemia is an example of a type 2 hypersensitivity reaction.
- Warm antibody autoimmune hemolytic anemia (AIHA) is the most common hemolytic anemia (70%) and is IgG-mediated.
- Cold agglutinin disease is less common (30%) and IgM-mediated (CM).
- Cold agglutination antibody in autoimmune hemolytic anemia is directed against reticulocyte. The causative auto-bodies are maximally reactive at 0-10 degrees Celsius
- The Reticulocyte count is the measure of effective Erythropoiesis. Corrected reticulocyte count <3% show ineffective Erythropoiesis (like beta Thalassemia) and more than or equal to 3% show effective Erythropoiesis.
- Reticulocytosis is most commonly seen in hemolytic anemia.
- Intravascular hemolysis is diagnosed by reticulocytosis
- Chronic hemolysis can lead to accumulation of endogenous pigment in the body called hemosiderin

#### **Chromosomal Translocation**

s/NO	Name of Diseases	Chromoso	omal Translocation
1.	CML	t(9;22)	(bcr-abl hybrid)
2.	Burkett's lymphoma	t(8;14)	(c-myc activation)
3.	Mantle cell lymphoma	t(11;14)	(cyclin D1 activation)
4.	Follicular lymphomas	t(14;18)	(bcl-2 activation)

## Acute Myeloid Leukemia (AML)

- · Auer rods: Fused azurophilic granules in the cytoplasm of Myeloblast
- Myeloperoxidase (MPO) and esterase positive,
- Gum hypertrophy and occur in Adult. DIC is common presentation
- It is associated with down syndrome

#### Chronic Myeloid Leukemia (CML)

- Sea blue histocyte
- Leukocyte alkaline phosphates (LAP) negative
- Leukocytosis, increase serum uric acid level
- Associated with Philadelphia chromosome, 9:22 translocation give BCR-ABL product
- Massive splenomegaly

#### Chronic Lymphocytic Leukemia (CLL)

- Smudge cell (Para chute cell), which are fragile leukemic cells
- Generalized painless lymphadenopathy and weight loss
- CD-19, CD-20 and CD-23 are the most common marker
- Associated with Autoimmune hemolytic anemia

#### Multiple Myeloma

- Multiple Myeloma: Monoclonal M-protein spike
- Rouleaux: "stack of coin" refer to erythrocyte lining up in row in blood smear
- Immunoglobulin (Ig) light chains in urine----Bence Jones protein
- Diagnostic investigation: Protein electrophoresis
- Clinical features: CRAB
  - ✓ C:-----Calcium.....HyperCalcemia (release from bone breakdown) which cause constipation and loss of appetite
  - ✓ R:----Renal failure

  - B: -----Bone pain and back pain—Punched-out Osteolytic bone lesions on X-ray. The lesion in the skull are called "rain-drop" lesion

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Page | 416 NASEEM SHERZAD FCPS - 1 HIGH-YIELD

#### Reed-Sternberg cells/HL

RS cells are derived from B-cells, are binucleated or bilobed with 2 halves as mirror image like "owl's eyes" and typically have brightly Esoinophillic nucleoli. RS are CD15+ and CD30+ B cell origin. The number of these cells and constituent of the background vary across HL subtypes. Background lymphocytes are usually T-cells.

## Hodgkin lymphoma

- Non-Hodgkin lymphoma is the most common (60%) while Hodgkin lymphoma is 40%
- Commonest node affected in Hodgkin lymphoma are cervical lymph nodes(rubbery consistency).
- The commonest type of leukemia that appears after treatment of HL is AML
- Hyperesonphilia occur in Hodgkin lymphoma
- Types of Hodgkin lymphoma(HL):
  - ✓ Nodular sclerosis HL: Commonest Hodgkin lymphoma is nodular sclerosis HL, Mediastinal. involvement is commonly seen in nodular sclerosis HL
  - ✓ Mixed cellularity HL: this is the 2<sup>nd</sup> most common
  - ✓ Lymphocyte predominant HL: Hodgkin lymphoma with the best prognosis is lymphocytepredominant HL
  - ✓ Lymphocyte depleted Hodgkin Lymphoma: this is the least common Hodgkin lymphoma. Hodgkin Lymphoma with worst prognosis & which is the most aggressive is lymphocyte depleted HL.
  - ✓ Morphology of nodular sclerosis:
    - o Bands of collagen: The bands are composed of dense collagen with interspersed small lymphocytes
    - o Lacunar type RS cells: Characteristic lacunar type of RS cells with distinctive pericellular halo is present.
    - The background usually contains several lymphocytes, histocyte, plasma cell eosinophils and neutrophil

#### Difference between Hodgkin and non-Hodgkin lymphoma

Hodgkin lymphoma	Non-Hodgkin lymphoma
Common in young adults	More common age40-70 years
It is mostly <b>localized</b> to a single axial group of nodes	It mostly involves multiple peripheral nodes
Contiguous spread	Non-contiguous spread
Extranodal involvement uncommon	Extranodal involvement common
Red-Sternberg cell present	Red-Sternberg cell absent
Mesenteric node and waldyer's ring are rarely involved	Mesenteric node and waldyer's ring commonly involved

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Chapter 16

Hematology

## **BLEEDING DISORDER**

The First rule, If there is a Problem in platelet, look for Bleeding time (BT) and if there is problem in factors, look for coagulation time (PT + APTT)

## Platelet-type of bleeding

## 1) Physiology of platelet:

- Clot retraction by------Thrombosthenin
- \* Prevent thrombus propagation by -------Heparin
- Therapeutic dose of heparin in DVT------5000 U S/C
- \* Platelet aggregation by-----TXA2---aspirin inhibit this
- Platelet adhesion by ------VWF
- . The best index of platelet is-----Clot retraction time
- Platelet half-life is------4-5 days
- Platelet life span------10 days

- Platelet is contraindicated in-----ITP
- Low molecular weight heparin (LMWH) inhibit------factor Xa
- Approximately 1/3 of platelet pool is stored in the-----Spleen
- All endothelial cell except those in cerebral microcirculation produce-----Thrombomodulin
- \* The most specific diagnostic test for heparin-induced thrombocytopenia is----serotonin release assay
- Platelet must be administrated within 4 hours, once the blood bag is opened by puncturing one of the sealed ports
- Megakaryoblast (megakaryocytes)------Platelets-----which contains

#### ✓ Dense granules:

- o ADP
- o Catt

#### √ Alpha granule

- o vWF
- o Fibrinogen,
- o PDGF

#### 2) Anticoagulant:

- Absolute contraindications to anticoagulation treatment include: intracranial bleeding, severe active bleeding, recent brain, eye, or spinal cord surgery, pregnancy, and malignant hypertension.
- Relative contraindications include: recent major surgery, recent cerebrovascular accident, and severe thrombocytopenia

#### 3) Pathology

- Platelet type of bleeding is mostly superficial (skin, mucous membrane) produce lesion like petechiae, ecchymosis, epistaxis and gingival bleeding.
- Only Bleeding time is increase in these diseases:
- ITP and TTP, these are platelet disorder so only bleeding time will be increase and remaining every things will be normal like PT and PTT.

#### Factor type of bleeding

- . The Factor type of bleeding is mostly deep (joint and muscle) producing the lesion like hemarthrosis and hematoma.
- \* PT and PTT will be increase. Bleeding time will be normal.

#### Extrinsic pathway:

- Include only Factor 7
- Prothrombin Time (PT): Test of extrinsic pathway(include only factor 7) and for warfarin monitoring
- WEPT mnemonic: PT test of Extrinsic pathway (Extrinsic factor is only 7) and use for warfarin monitoring. NOTE: for oral anticoagulant like warfarin INR>>>>PT

#### Intrinsic pathway

Partial Thromboplastin Time (PTT): Test of the intrinsic pathway (intrinsic factors are 8-9-11-12), to remember count from 8 to 12 by skipping 10. So PTT is the real player because there are a lot of disease in which there is the deficiency in these factor best example is hemophilia A and B so the one and only one PTT will be increase remaining every things will be normal

#### Common pathway

- Intrinsic and extrinsic pathway converge on factor 10
- The Factors of the common pathway are: 1, 5 and 2, 10 (can be remembered by one five and two five ten) extrinsic pathway having only 7 and remaining all factors are in the intrinsic pathway. (Extrinsic: only 7, intrinsic: 8,9,11,12 common pathway: 1, 5 and 2, 10)
- Deticiency in common pathway factor increase both PT and PTT like vitamin k deficiency (vitamin K dependent factor 2, 7, 9, 10)

#### Activation:

- Factor 12 (Hageman factor) is activated by subendothelial injury or collagen exposure which in turn active intrinsic pathway, begin in blood itself
- The Extrinsic pathway is activated by tissue factor or tissue Thromboplastin or contact activation and released from traumatized tissue, begin by blood vessels or surrounding tissue
- Activation of extrinsic or intrinsic pathway cause activity of common pathway----
  - ✓ Factor II (Prothrombin)----- Ila (thrombin)
    - o Converted by 10a and 5a acted as a cofactor
  - ✓ Fibrinogen (I)-----fibrin (Ia)

Converted by thrombin (IIa)

- Conversion of fibrinogen into fibrin, decrease fibrinopeptides can be detected in blood
- Factor 13 or fibrin stabilizing factor is the enzyme that cross-link fibrin
- t-PA cause conversion of plasminogen into plasmin which causes fibrinolysis

#### & Von willebrand disease:

Factor 8 and von Willebrand factor both are decrease so bleeding time will be prolonged (von Willebrand factor) and PTT will also be prolong (factor 8 deficiency)

#### A Pathology

- Hemophilia A is also called classic hemophilia or factor VIII deficiency.
- Hemophilia B is also called Christmas disease or factor IX hemophilia.
- Von Willebrand disease is the most common inherited coagulation disorder.

#### Factor V Leiden Mutation:

- Factor V Leiden mutation is the most common Prothrombotic genetic defect.
- It accounts for 40 to 50% of all cases of inherited thrombophilia.
- Biochemically, the etiology of the factor V Leiden mutation is point mutation resulting in an Arginine to glutamine substitution at position 506 in coagulation factor V.
- It is the most common cause of hereditary thrombophilia.
- Where the most common cause of acquired thrombophilia is an anti-phospholipids syndrome
- Clotting factor 12 deficiency or factor V Leiden mutation Causes thrombosis more than bleeding. Individuals who are homozygous for factor V Leiden have a high incidence of thrombosis.

#### Protein C deficiency:

- Protein C deficiency increases the risk of developing abnormal blood clots; the condition can be mild or severe.
- Individuals with mild protein C deficiency are at risk of developing DVT deep vein thrombosis (DVT).
- condition in which skin and subcutaneous skin necrosis is a Warfarin-induced tissue necrosis (tissue death) occurs due to acquired protein C deficiency following treatment with warfarin

#### Factor 8:

- \* Factor 8 has two components, small component which is deficient in hemophilia A and large component which is deficient in Von Willebrand disease.
- Factor 8 produce by:
  - ✓ Endothelial cell---all over the body
  - ✓ And Sinusoidal cell of liver
  - ✓ In liver failure clotting factors are low except factor 8 which is paradoxical supra-normal because it is synthesized by the endothelial cell through the body and for clearance of activated factor 8 good hepatic function is required, leading to increased circulating level of factor 8

Chapter 16

Summary

- . Hemophilia A+B PLUS clinical features of deep bleeding(hemarthrosis and hematoma):
  - ✓ Only and only look for APTT and that will be rise remain every things will be normal(normal APTT is 26-36 sec)
- . ITP and TTP+ clinical feature of superficial bleeding (epistaxis, petechiae ,ecchymosis and vaginal bleeding)
  - ✓ Only and only focus on bleeding time and that will be rise remain everything's will be normal(Normal BT is 8-10 min)
- Von willebrand disease:
  - ✓ Only bleeding time and APTT will be increase remain every things will be normal.
- Disseminated intravascular coagulation (DIC)
  - Everything will be rise except platelet and fibrinogen which will be decreased
  - Caused by stimulation of Thromboplastin
  - D-dimer is overall diagnostic/Most specific test and Most sensitive test is FDP
  - ✓ The bleeding diathesis in patients with acute promyelocytic leukemia (APL) is generally attributed to disseminated intravascular coagulation (DIC), initiated by the release of procoagulant activity from leukemic cells.

#### Coumarin derivatives

- Dicurmarol
- Warfarin(Coumadin)
- Differences:
  - o Rodenticides (Rat poison) block vitamin K cycle, effect same as warfarin overdose
  - There is Increase PT in Coumarin derivatives overdose and Rodenticides

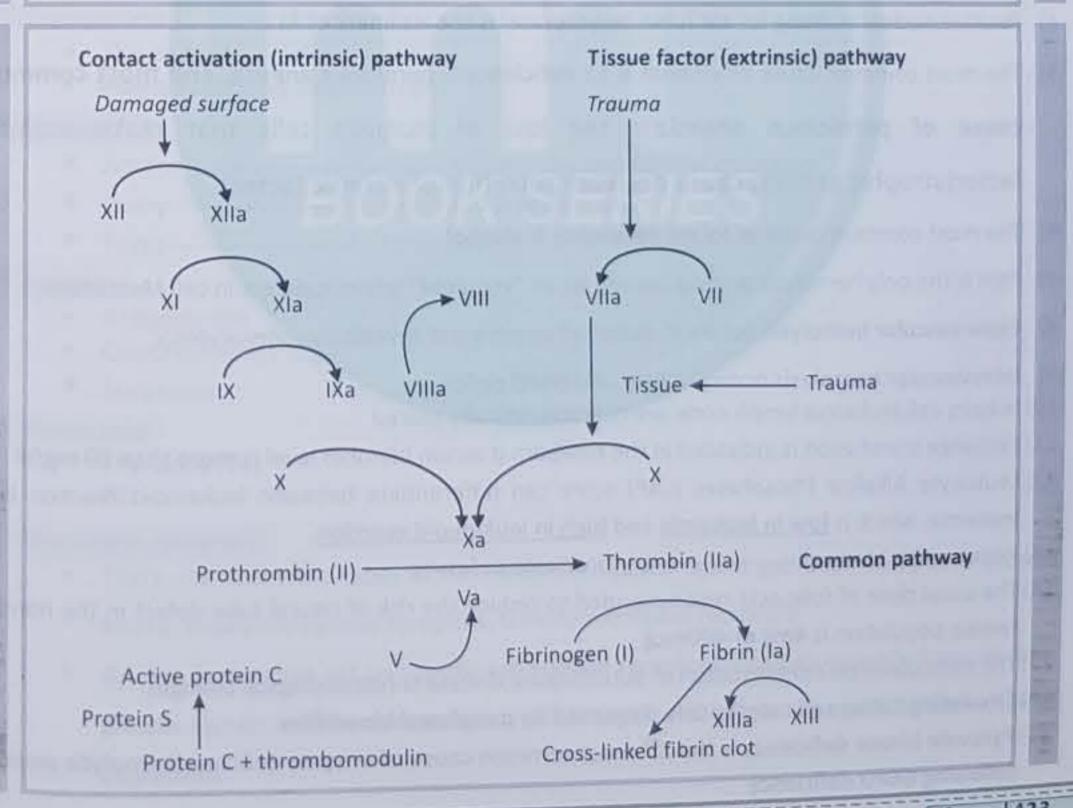
#### Dimercaprol (BAL):

- ✓ Use for acute toxicity of lead and mercury
- ✓ Cause thrombocytopenia so there will be increase in bleeding time

#### Heparin Vs warfarin

S.NO	Heparin	Warfarin
1.	Activate antithrombin III	Inhibit vit-K dependant factors
2.	Act on factor IIa and 10a	Inhibit factor II and 10
3.	Natural anticoagulant	
4.	Can cause alopecia and increase in lipoprotein lipase	Warfarin can cross placenta while heparin cant cross
5.	Rout: Parenteral	Route: Oral
6.	Overdose treatment:	Overdose treatment: Vit-K and fresh frozen plasma

**Coagulation Cascade** Intrinsic pathway Extrinsic pathway Tissue factor VIII Common aPartial Prothrombin pathway Thromoboplastin Time Time ca++ Lipids Prothrombin (ii) → Thrombin Fibrinogen (I) → Fibrin clot (XIII)



#### Congenital And Acquired Hypercoagulable States

Congenital	Acquired
<ul> <li>Factor V leiden mutation</li> </ul>	<ul> <li>Anti-phospholipid antibody syndrome</li> </ul>
Proetin C deficiency:	Malignancy (like Ca pancreas)
<ul> <li>Protein S deficiecny</li> </ul>	<ul> <li>Surgery/trauma</li> </ul>
Antithrombin III deficiency	Pregnancy/oral contraceptives
Hyper-homocysteinemia	<ul> <li>Prolonged immobilization</li> </ul>
<ul> <li>Dysfibrinolysis</li> </ul>	Older age

#### **HIGH YIELD POINTS**

- The most common cancer in children is leukemia
- The Most common leukemia in children is ALL.
- 3) The Most common leukemia in the adult is AML.
- Positive nuclear staining for tdt (DNA polymerase) is the Hallmark of ALL.
- The most common cause of vitamin B-12 deficiency is pernicious anemia. The most common cause of pernicious anemia is the loss of stomach cells that make intrinsic factor(atrophic gastritis cause decrease secretion of intrinsic factor)
- The most common cause of folate deficiency is alcohol.
- PNH is the only hemolytic anemia caused by an "acquired" intrinsic defect in cell Membrane.
- Extra-vascular hemolysis occurs in sickle cell anemia and hereditary spherocytosis.
- Intravascular hemolysis occurs in PNH and G6PD deficiency.
- 10) In hairy cell leukemia lymph node are characteristically spared
- 11) Exchange transfusion is indicated in the newborn if serum bilirubin level is more than 20 mg/dl
- 12) Leukocyte Alkaline Phosphates (LAP) score can differentiate between leukemoid reaction and leukemia, which is low in leukemia and high in leukemoid reaction.
- 13) Anemia with blast cell----erythroblastosis fetalis
- 14) The usual dose of folic acid recommended to reduce the risk of neural tube defect in the normal female population is 4mg or 400mcg
- 15) The most common manifestation of autoimmune disease is hematological changes
- 16) Circulating tumor cell most widely diagnosed by peripheral blood film
- 17) Pyruvate kinase deficiency is the 2<sup>nd</sup> most common cause of enzyme deficient hemolytic anemia following G6PD deficiency

# ENDOCRINE 17 SYSTEM

## Classification of Hormones and Receptors

#### Peptides e.g.

- Anterior pituitary hormones-----GH, ACTH, Prolactin
- Posterior pituitary hormones-----ADH and oxytocin
- Pars intermedia of pituitary gland -----alpha and beta MSH
- Islets of Langerhans -----insulin, glucagon, and Somatostatin
- Parathyroid hormones
- Thyroid gland----Calcitonin
- Releasing and inhibitory hormones and factors of the hypothalamus
- GIT hormones
- Ovary----relaxin
- All peptides hormones bind to receptors in the plasma membrane of the target cells

#### Glycoprotein:

- TSH and LH
- Human chorionic Gonadotropin

#### Steroids:

- Adrenal cortex------Cortisol, Aldosterone and adrenal androgen
- Ovary-----Estrogen and progesterone
- Testis-----Testosterone

#### Amines:

- Acetylcholine
- Catecholamines
- Melatonin

#### Mamino acid:

- Thyroxine (T4)
- T3

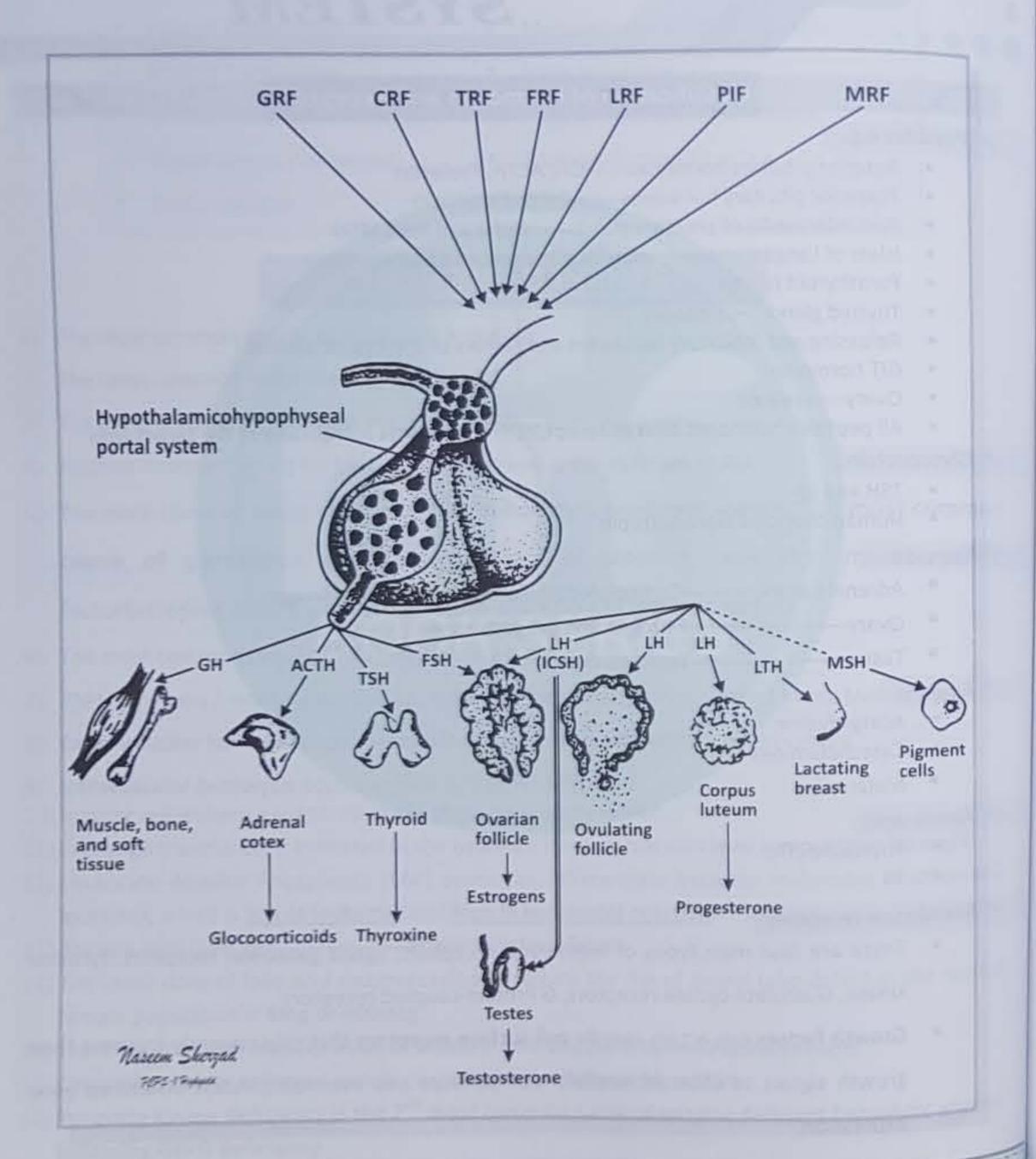
#### Membrane receptors:

- There are four main types of membrane receptors: ligand gated-ion receptors, tyrosine kinase, Guanylate cyclase receptors, G Protein-coupled receptors
- Growth factors can act on specific cell surface receptors that subsequently transmit their growth signals to other intracellular components and eventually result in altered gene expression.

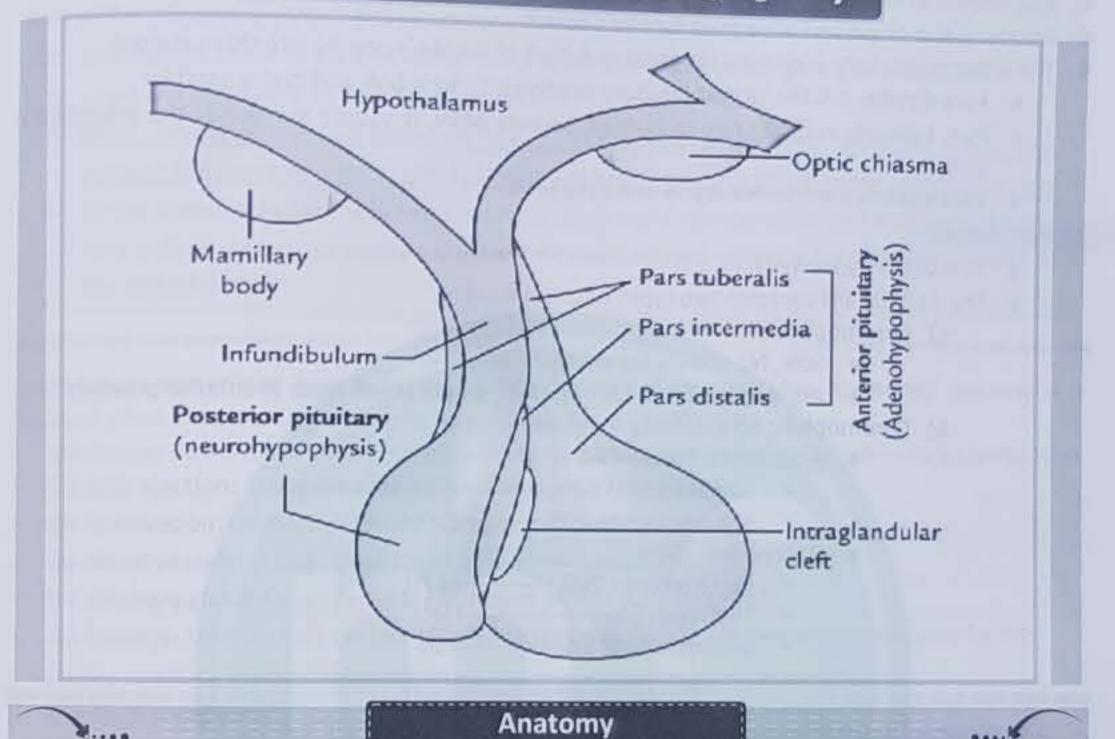
#### **Endocrine System**

#### Second messenger as cyclic AMP:

- ADH, Calcitonin and glucagon
- FSH, LPH, LH, MSH, PTH and TSH
- Somatostatin and chorionic Gonadotrophin hormones



## Pituitary Gland (Hypophysis)



- Location: Lies in the Hypophyseal fossa in the sella turcica of sphenoid bone with the <u>diaphragm</u> sella above it
- It is called the master gland because it produces hormones that control other gland and many body functions including growth
- Pituitary gland consists of three-lobe: in most species, the pituitary gland is divided into three
  lobes anterior, posterior and intermediate lobe
- Melanotropin: Secreted by the intermediate lobe of the hypophysis in human
- Surgical Removal of the pituitary gland can cause amenorrhea
- \* Relations:
  - ✓ Anteriorly: Sphenoid sinus
  - ✓ Posteriorly: Dorsum sella, basilar artery and Pons
  - ✓ Superiorly: Diaphragm sella and Optic Chiasma
  - ✓ Inferiorly: The body of the sphenoid and sphenoid sinus
  - ✓ Laterally: The cavernous sinus and its contents
- \* Blood Supply: The Blood-Brain barrier is absent in the pituitary gland
  - Hypophyseal arteries---arise from internal carotid artery and circle of Willis, inferior Hypophyseal artery (supplies Neurohypophysis) and superior Hypophyseal artery (supplies Pars tubers, median eminence and infundibular stem)
  - ✓ Venous drainage: veins from anterior and posterior pituitary gland drain into the cavernous sinus

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· Ectodermal in origin and arise from Rathke's pouch

. The anterior pituitary is divided (by residual lumen of Rathke's pouch) into three regions

· Pars distalis: it is the largest pituitary subdivision, main bulk and highly vascular

 Pars tuberalis-rudimentary in human, secrete MSH, it usually surrounds the infundibular stalk

Pars intermedia---Secret Alpha and Beta MSH

#### Pars distalis

75% of the hypophysis

The Pars distalis contains two types of cells including:

a) Chromophobes:

• 50%, No affinity for stains

· Are degranulated Chromophils, smallest cell types in anterior pituitary

b) Chromophils: 50%, affinity for stain

Acidophils: 70%----PAG

✓ Somatotropes 50%------Growth hormone

✓ Mammotropes 20%-----Prolactin

♦ Basophiles---30%

✓ Corticotropes 20%-----ACTH

✓ Thytropes 5%----TSH

√ Gonadotropes 5%-----FSH

#### **Posterior Pituitary Gland**

Also known as Neurohypophysis

Neuroectodermal in origin and arise from the hypothalamus

It consists of:

Axon—unmyelinated fiber from the hypothalamus

Axon from supraoptic nuclei (SON) secrete ADH

Axon from paraventricular nuclei secret----oxytocin

✓ Supporting the neuroglial cell called Pituicytes

✓ Blood vessels

Hormone (ADH, oxytocin) are synthesized in Hypothalamic nuclei (cell bodies), travel in the axon
to the posterior pituitary, where they are stored (not synthesized) and released into circulation

 The posterior pituitary gland does not produce hormones, but rather stores and secrete hormones produced by the hypothalamus

Parts: The neurophysis is consists of two parts

✓ Pars nervosa: Also called the neural lobe or posterior lobe, this region constitutes the majority of the posterior pituitary and is the storage site of oxytocin and vasopressin. Sometimes (incorrectly) considered synonymous with the posterior pituitary, the pars nervosa includes Herring bodies and pituicytes.

✓ Infundibulum: The infundibulum is formed by two structures 1) the median eminence, a funnel-shaped extension of the hypothalamus and 2) the infundibular process

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Neurophysins I——Oxytocin

Neurophysins II----ADH

Chapter 17

Endocrine System

## Naseem Sherzad High-Yield Points: ACTH

ACTH is released by releasing hormones from the hypothalamus

\* ACTH effectively control hydrocortisone

The highest concentration of ACTH found in venous blood, drainage anterior pituitary

Small cell carcinoma of lung produce ACTH

Most potent stress hormone cortisol > ACTH, but when they mention stress plus vasoconstriction then select catecholamine because it the only which cause vasoconstriction

Stress stimuli activate the entire system to cause rapid release of cortisol and the cortisol in turn initiate a series of metabolic effects directed toward relieving the damaging nature of the stressful state

#### **Oxytocin Function**

Oxytocin is sometimes known as the "cuddle hormone" or the "love hormone," because it is released when people snuggle up or bond socially.

On uterus: Powerfully stimulate pregnant uterus toward the end of gestation----helps parturition

On milk ejection: Cause increase milk ejection in lactating breast

On fertilization: Oxytocin released during coitus by nervous reflex

On blood vessels: In large dose cause vasodilation and decrease BP

On pituitary gland: Cause prolactin secretion, inhibit ADH secretion

 On kidneys: Infusion rate greater than 20mU/min can decrease free water clearance by the kidney resulting in water intoxication

Oxytocin receptors:

✓ The activity of this receptor is mediated by G-proteins, which activate a phosphatidylinositol-calcium second messenger system.

Oxytocin receptors are expressed by the myoepithelial cells of the mammary gland, and in both the myometrium and endometrium of the uterus at the end of pregnancy.

✓ Oxytocin receptors are also present in the central nervous system.

#### Growth Hormone (GH)

Also called somatotropin or somatotropic

NAME AND POST OFFICE ADDRESS OF TAXABLE PARTY.

it is single-chain polypeptide that is homologous with prolactin and human placental lactogen

Growth factor receptors are presents on the plasma membrane

Somatostatin is the inhibitory counterpart of Growth Hormone Releasing Hormone.

Growth hormone is released in the pulsatile fashion

Action on protein metabolism------Anabolic

Action on fat metabolism-----lipolytic

Action on carbohydrate metabolism-----Cause hyperglycemic

\* Action on cartilage and bones:

✓ GH act on liver———Somatomedin also called IGF—formed by liver—act on cartilage and bone to stimulate their growth

GH Convert Chondrocytes into Osteogenic cells thus causing deposition of new bone

✓ Growth hormone strongly stimulate osteoblast, therefore the bone become thicker throughout the life

Chapter 17

#### Circadian Rhythm:

- ✓ Growth hormone is released during deep sleep
- ✓ Cortisol release is highest in the morning and drops during the day, released during times
  of stress, possibly why it is hard to sleep when stressed
- ✓ For circadian rhythm, optic nerve send fibers to Suprachiasmatic nucleus

#### Secretion is increased by: 3S

- √ Sleep
- ✓ Stress, Starvation
- ✓ Exercise
- √ Hypoglycemia

#### Secretion is decreased by: SHOP

- ✓ Somatostatin
- ✓ Somatomedin
- ✓ Hyperglycemia
- ✓ Obesity and
- ✓ Pregnancy (decreased or normal)

#### Pathology

#### 1) Hyperpituitarism:

- \* Refer to excess secretion of pituitary hormone:
- It is most commonly caused by the pituitary adenoma of the anterior lobe, such as:
  - 1. Prolactinoma (most common functioning adenoma)
  - 2. Growth hormone adenoma (2<sup>nd</sup> most common)
  - 3. Thyrotroph adenoma
  - 4. ACTH-producing adenoma
  - 5. Gonadotroph adenoma
- The Patient of hyperpituitarism can present with Sign and symptoms of vaginal bleeding.
   Hirsutism, decrease libido, headache, muscle weakness, visual field loss or double vision etc.

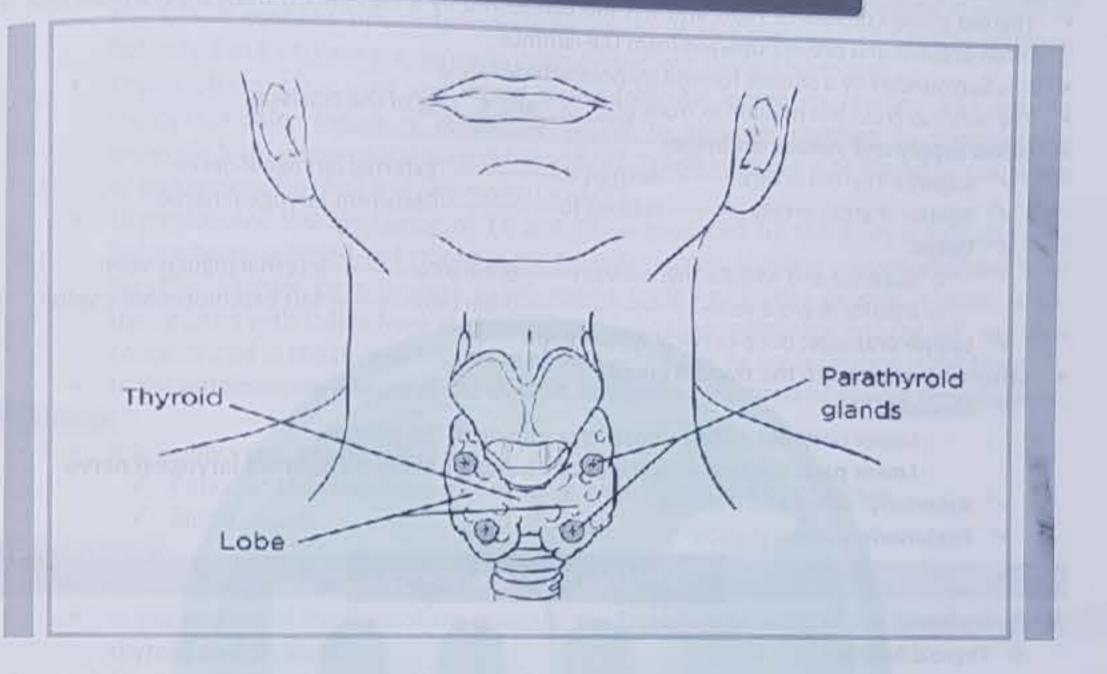
#### 2) Hypopituitarism

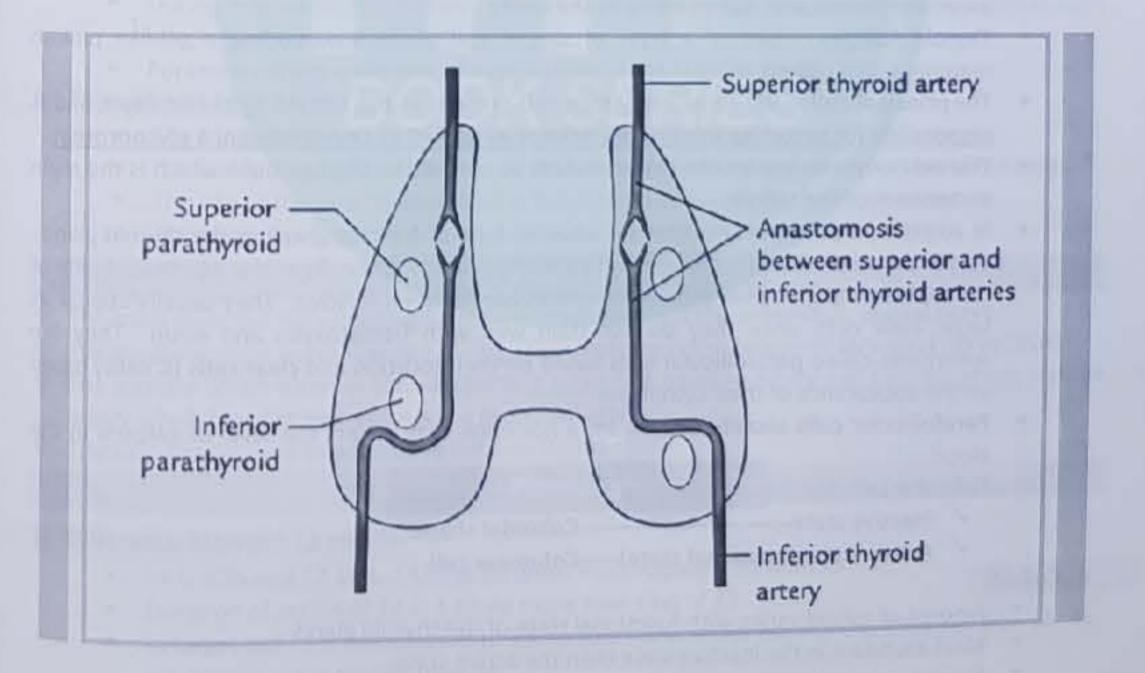
- It refers to decrease secretion of the pituitary hormone.
- It occurs when 75% of pituitary parenchyma is lost or absent.
- · Cause:
  - ✓ The most common cause in children=Craniopharyngioma
  - ✓ The most common cause in adult =Non-functioning adenoma
  - ✓ Empty sella syndrome---empty sella turcica that is not filled with pituitary tissue
  - ✓ Pituitary apoplexy---Sudden hemorrhage into pituitary gland often in pituitary adenoma
  - ✓ Sheehan syndrome----Refer to postpartum necrosis of anterior pituitary gland (clinical feature include Inability to lactate and menstruate)

#### 3) Acromegaly:

- \* The most common cause of death in Acromegally is heart failure from cardiomyopathy.
- · Acromegaly occurs due to an increase in growth hormone level after the closure of epiphysis.
- · Gigantism occurs due to an increase in growth hormone before the closure of epiphysis.
- \* The Best initial test for Acromegaly is insulin-like growth factor (IGF)

## **Thyroid Gland**





- Thyroid gland consists of right and left lob connected by a narrow isthmus, a pyramidal lobe is often present and project upward from the isthmus
- It is Surrounded by a sheath formed by pretracheal fascia
- The isthmus cross the midline in front of 2<sup>nd</sup>, 3<sup>rd</sup> and 4<sup>th</sup> ring of the trachea
- Blood supply and venous drainage:
  - -- External laryngeal nerve ✓ Superior thyroid artery——related to———
  - -- Recurrent laryngeal nerve ✓ Inferior thyroid artery----related to-----
  - √ Veins:
    - o Superior and Middle thyroid vein-----drain into------Internal jugular vein
    - -left brachiocephalic vein -----drain into-o Inferior thyroid vein----
  - ✓ Lymph drainage: deep cervical lymph node
- Structural relations to the thyroid gland
  - ✓ Medially:
    - o Upper part: the middle constrictor muscle of the pharynx
    - o Lower part: trachea, esophagus and between them is recurrent laryngeal nerve
  - Anteriorly: infrahyoid muscles
  - Posteriorly: carotid sheath

Histology and Embryology

#### 1) Parenchyma:

- Thyroid follicle:
  - These are irregular spherical bodies made of a single layer of epithelial cell, resting on the basement membrane, surrounding by the cavity
  - . Thyroid follicles consist of a layer of simple epithelium surrounding a gel-like pinkish material called colloid.
  - The principal cell is the most numerous cell present in the simple epithelial layer and is responsible for secreting the thyroid hormones as well as thyroglobulin, a glycoprotein.
  - Thyroid hormones are stored extracellularly as part of the thyroglobulin which is the main component of the colloid.
  - In addition to principal cells there is another type of functional cell in the thyroid gland. This is the parafollicular cell, which may be found as single cells in the epithelial lining of the follicle or in groups in the connective tissue between follicles. They usually appear as large, clear cells since they do not stain well with hematoxylin and eosin. They are sometimes called parafollicular cells based on their location and clear cells (C cells) based on the appearance of their cytoplasm.
  - Parafollicular cells secrete Calcitonin, a hormone that lowers the level of calcium in the blood
  - Follicular cell depends on the state of functional activity
    - ✓ Inactive state-----Cuboidal shape
    - ✓ Active state (functional state)----Columnar cell
- Colloid:
  - Amount of colloid varies with functional state of the thyroid gland
  - Most abundant in the inactive state than the active state
  - Consist mainly of thyroglobulin

Chapter 17

**Endocrine System** 

#### # Thyroid hormones synthesis:

- Thyroglobulin is a glycoprotein made up of two subunits and has a molecular weight of 660 kDa. It contains 10% carbohydrate by weight. It also contains 123 tyrosine residues, but only 4 to 8 of these are normally incorporated into thyroid hormones
- Thyroglobulin is secreted and stored in the follicular lumen via reaction with enzyme thyroperoxidase. lodine is covalently bound to tyrosine residues in thyroglobulin molecule form monoiodotyrosine (MIT) and DIT. Triiodthyronine is produced by combining of one molecule of MIT and one molecule of DIT
- Thyroglobulin, the pre-cursor of T4 and T3, is produced by the thyroid follicular cells before being secreted and stored in the follicular lumen. lodide is actively absorbed from the bloodstream by a process called iodide trapping. In this process, sodium is cotransported with iodide from the basolateral side of the membrane into the cell, and then concentrated in the thyroid follicles to about thirty times its concentration in the blood.
- In the autoimmune disease of the thyroid, antibodies are directed against thyroglobulin

#### 2) Stroma:

- It is highly vascular and consists of:
  - ✓ Reticular connective tissue containing lymphocyte and macrophage
  - ✓ Blood vessels

#### 3) Embryology:

- It is the first gland, which appears about 24 days after fertilization
- In the midline of the floor of the pharynx, the Endodermal lining of the foregut form the thyroid diverticulum
- Migrate caudally to the hyoid bone and laryngeal cartilage
- During migration, the thyroid remains connected to the tongue by the Thyroglossal duct, which later obliterated
- Foramen cecum is the site of evagination of the thyroid gland

#### 4) Thyroglossal cyst:

- The Most common site of Thyroglossal cyst is infrahyoid
- It is freely mobile from side to side and rises on swallowing and protrusion of the tongue
- The site of the Thyroglossal duct is indicated in the adult by the foramen cecum.
- Treatment: Surgical excision by Sistrunk's procedure

#### **Clinical Notes**

The most common nerve damage during thyroidectomy is the external la yngeal nerve.

- The most common nerve damage during Tracheostomy is the recurrent laryngeal nerve (RLN)
- The arteries which bleed in tonsillectomy is ascending palatine artery and tonsillar artery and the artery which bleed in hemoptysis is a bronchial artery.
- \* Thyroxin can be used as adjunctive for depression

## Physiology

#### 1) Difference between T3 and T4

- T4 is 90% and T3 10%, T4 bind 10 times more rapidly TBG than T3
- Duration of action of T4 is 4 times more than that of T3
- In target cell T4 is deiodinated to T3, so true intracellular hormone is T3 rather than T4. T3 act 4 times more rapidly than T4
- The active form of thyroxin is free or unbounded form

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- Ectopic thyroid hormone is produced by squamous cell carcinoma of larynx
- lodine from thyroiditis mostly loss through urine
- 2) Fluctuations in Deiodination:
  - Much more RT<sub>3</sub> and much less T<sub>3</sub> are formed during fetal life, and the ratio shifts to that of adults about 6 wk after birth. Various drugs inhibit deiodinases, producing a fall in plasma T<sub>3</sub> levels and a reciprocal rise in RT<sub>3</sub>.
  - Selenium deficiency has the same effect.
- 3) Chemistry and metabolism of TSH
  - Human TSH is a glycoprotein that contains 211 AA residue
  - The biologic half-life of human TSH is about 60 min. TSH is degraded for the most part in the kidneys and to a lesser extent in the liver. The Secretion is pulsatile, and the mean output starts to rise at about 9:00 PM, peaks at midnight, and then declines during the day.
- 4) The action of T3 and T4:
  - On protein metabolism:
    - ✓ T3 and T4 increase protein synthesis, Increase intracellular enzyme
  - On carbohydrate
    - ✓ Increase glucose absorption from GIT, Increase insulin secretion.
    - ✓ Increase Glycolysis and Gluconeogenesis
  - On fat metabolism:
    - ✓ Increase metabolism of fatty acid from adipose tissue
    - ✓ Increase in free fatty acid concentration in plasma
  - On mitochondria:
    - ✓ Increase in No. and size of mitochondria
    - ✓ Increase the activity of mitochondria and increase ATP formation
  - " On growth:
    - ✓ T3 and T4 promote growth because they promote protein synthesis
  - Fetal brain:
    - ✓ Cause fetal brain development

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S.NO	Hypothyroidism	Hyperthyroidism
1.	Cold intolerance	Heat intolerance
2.	Weight gain, decrease appetite	Weight loss, despite increase appetite
3.	Constipation	Diarrhea
4.	Decrease reflexes, Carpal tunnel syndrome	Increase reflexes, anxiety, irritability
5.	Menorrhagia	Oligomenorrhoea
6.	Bradycardia, dyspnea on exertion	Palpitation, chest pain, arrhythmia
7.	Dry, cool skin, coarse, brittle hair	Warm, moist skin, fine hair
8.	Increase TSH, decrease free T4, Increase cholesterol level	Decrease TSH, increase total or free T3,

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Some Confusing Terminology



**Endocrine System** 

#### pretibial myxedema:

- Also called infiltrative dermopathy
- It is the thickening of the skin around the Pretibial and dorsum of the foot
- . Seen in Graves' disease
- Caused by immune-mediated process conducted by TSH receptor antibody

#### Myxedema:

- Also called Gull disease
- It refers to hypothyroidism developing in late childhood or adults.

#### 3) Cretinism:

- Also called infantile hypothyroidism
- It refers to hypothyroidism developing during fetal and neonatal development
- Two important clinical feature, Macroglossia (large tongue) and umbilical hernia
- Two types
  - ✓ Endemic Cretinism (15% of cases): When due to iodine deficiency
  - ✓ Sporadic Cretinism (85% of cases): Due to congenital enzyme (TPO-thyroid peroxidase) deficiency or thyroid agenesis

#### 4) Thyrotoxicosis:

Thyrotoxicosis is a hypermetabolic state caused by the elevated circulating levels of free T3 or T4 with OR without hyperthyroidism.

#### 5) Hyperthyroidism:

Hyperthyroidism is a type of Thyrotoxicosis in which excess of hormone is due to increased synthesis by the hyperfunctioning thyroid gland.

- 6) Thyroid binding globulin (TBG): Increase in TBG levels like in pregnancy or decrease in TBG level like in hepatic failure cause decrease or increase in total thyroid level but having no effect on free hormone means free T<sub>4</sub> or T<sub>3</sub> remains normal.
- **Endemic** goiter

Endemic goiter is a type of goiter that is associated with dietary iodine deficiency and it is called endemic when more than 10% population is involved in the given area.

#### 8) Retrosternal Goiter:

- A goiter with the portion of its mass located in the mediastinum
- Growth of the goiter may cause dyspnea (worse on lying flat) due to tracheal displacement
- Dysphagia due to esophageal compression
- Voice changes due to recurrent laryngeal nerve pressure

## Grave's Disease

- It is a type II hypersensitivity reaction.
- Thyroid-stimulating immunoglobulin (TSI) or TSH receptor antibody (TRab) which mimics the action of TSH, causing continuous stimulation of thyroid gland, It can be detected in the serum of 80% to 95% of patient with Graves' disease

- It is the most common cause of endogenous hyperthyroidism under age 50
- (protrusion of the eyes) + dermopathy + audible bruit
- Exophthalmos and pretibial myxedema in graves is not due to hyperthyroidism but due to antibody (TSI) that stimulates TSH receptors. These TSH receptors are also found on fibroblasts located behind the eye as well as over the sheen. In response to these antibodies, fibroblast secrete excess glycosaminoglycan (Gag) which result in Exophthalmos and pretibial myxedema Most probable treatment to relieve Exophthalmos is to give the drug that reduces T cell activation.
- Note: Struma Ovarii cause hyperthyroidism by secreting T3, T4 or TSH

## Hashimoto's thyroiditis or chronic lymphocytic thyroiditis



- Hashimoto thyroiditis (an autoimmune disorder) is the most common cause of hypothyroidism in areas of the world where iodine levels are sufficient
- Anti-thyroid Peroxidase antibody are present in the serum of more than 90% of patient with Hashimoto's Thyroiditis.
- Anti-thyroglobulin antibody = positive
- The most common cause of hypothyroidism
- B-cell non-Hodgkin lymphoma (very important), type 1 diabetes and Myasthenia gravis are the most common complication of Hashimoto's thyroiditis.
- Caused by break down of self-tolerance to thyroid autoantigen
- This is the autoimmune disease in which a single organ involved

## Types of Hypothyroidism (From bottom to Top)



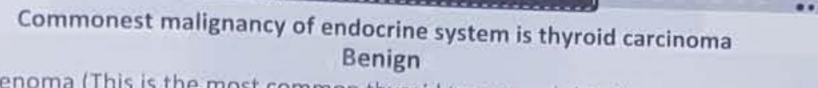
- Primary Hypothyroidism: it is the most common. it is due to disease in the thyroid and TSH levels are high
- Secondary Hypothyroidism: it is less common. it is due to pituitary disease and TSH level is Low
- Tertiary hypothyroidism: Tertiary hypothyroidism is characterized by abnormally low level of T3 and T4 Production, where the defect is at the level of the hypothalamus. TRH stimulation test: An increase in the serum TSH level following TRH administration means that the cause of hypothyroidism is in the hypothalamus (tertiary Hypothyroidism), i.e. the hypothalamus is not producing TRH. Therefore, when TRH is given exogenously TSH level increase

#### **Thyroid Function Test**

- TSH is the most useful and sensitive investigation of thyroid hormone function both for hyperthyroidism and hypothyroidism (v.very imp)
- The best marker to monitor the thyroid status of the hypothyroid patient who is on thyroxin is TSH
- TSH is elevated in hypothyroidism and decreased in Hyperthyroidism.
- Free or unboundedT4 and T3 decreased in hypothyroidism and elevated in hyperthyroidism
- Negative feedback between TSH and T3, T4

## Classification of Thyroid Tumors

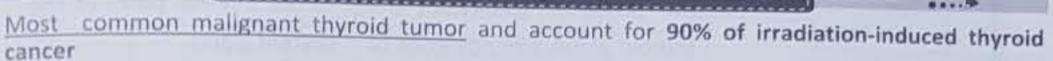
## **Endocrine System**



- Follicular adenoma (This is the most common thyroid tumor and this the most common benign tumor of the thyroid)
- Hurthle cell adenoma
- Colloid adenoma

#### Malignant

#### Papillary carcinoma--- (p-opular)...most common



- LymPhatic spread occurs first and hematogenous spread to the lung is most common.
- It is the most slow growing malignancy of thyroid and having the best prognosis.
- · Morphology:
  - ✓ "Orphan Annie eye" nuclei or ground glass i.e. empty appearing nuclei (diagnostic) feature)
  - Pseudo inclusion----intranuclear inclusions
  - Psammoma bodies .i.e. dystrophically calcified cancer cell

#### Follicular carcinoma

- 2<sup>nd</sup> most common thyroid cancer.
- Most frequently occur in the area with dietary iodine deficiency and endemic goiter regions.
- Capsular or vascular invasion differentiate it from follicular adenoma, which is a benign condition.
- Hematogenous spread occurs first

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#### Medullary carcinoma

- · Amyloid deposit derived from altered Calcitonin molecule are present in the adjacent stroma in many cases and distinctive feature
- Amyloid in Medullary carcinoma thyroid is confirmed by a special stain Congo red.
- Medullary carcinoma is neuroendocrine neoplasm derived from the parafollicular cells or C cells of the thyroid
- Serum Calcitonin is a tumor marker in-patient with Medullary carcinoma, which is valuable in the follow-up of a patient with post-resection.
- It is associated with MEN II syndrome.
- Diarrhea is present in 30% cases.
- It is sporadic in about 70% of cases the remaining 30% are familial.
- Familial Medullary thyroid carcinoma-----Bilateral
- Sporadic Medullary thyroid carcinoma----Solitary nodule

#### Anaplastic carcinoma

- It is the most aggressive tumor with a mortality rate is 100%,
- it has the worst prognosis of all thyroid tumor with the median survival rate is 3 months
- The cause of death is the compression of vital structure in the neck.

## **Parathyroid Gland**

#### **Anatomy**

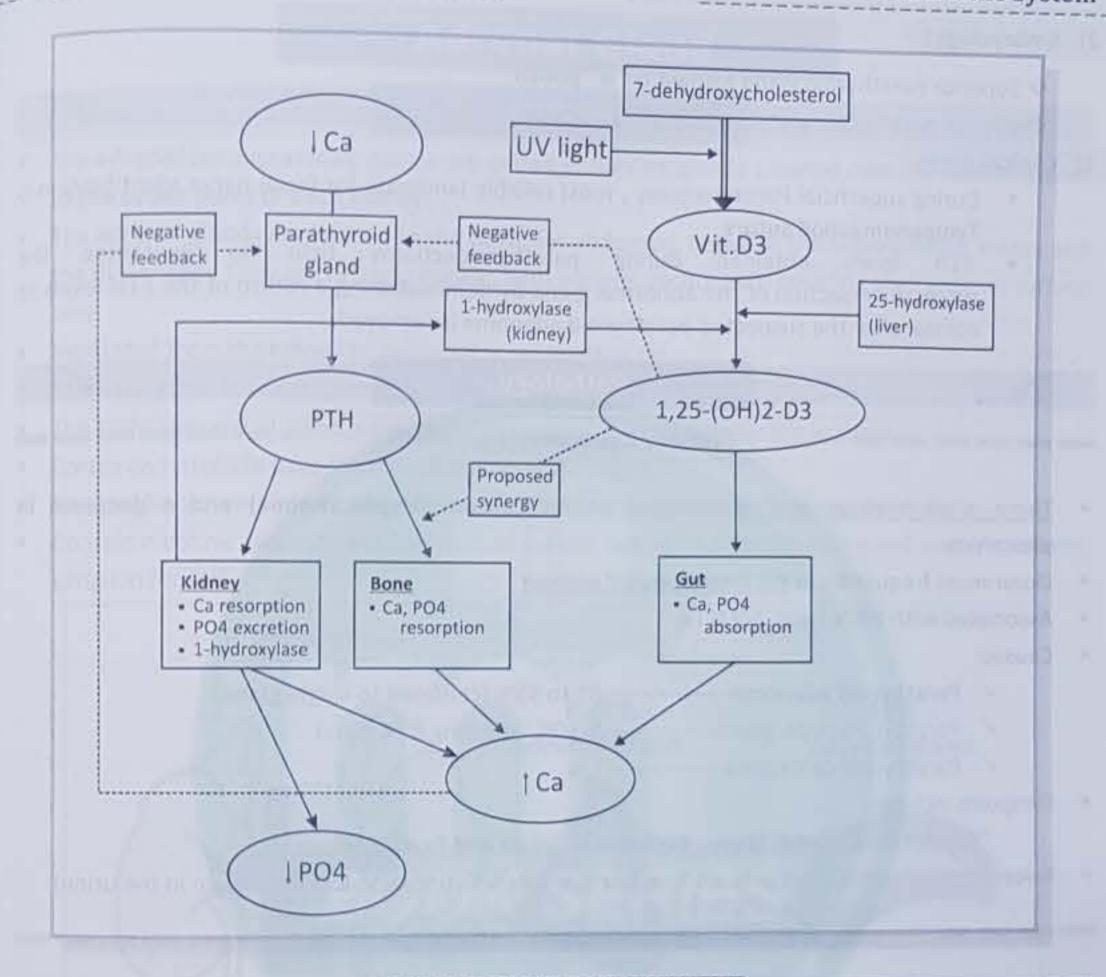
	Superior Parathyroid gland	Inferior Parathyroid gland
Location	The two superior parathyroid gland lies behind the middle of the posterior surface of the thyroid gland, lies posterior to Recurrent laryngeal nerve and cranial to Inferior thyroid artery	The two inferior parathyroid gland lies close to the inferior poles of the thyroid gland
Position	More constant in its position	Variable in its position
Size	Small	Large
Blood supply	The parathyroid gland are usual inferior thyroid arteries, but to superior thyroid arteries; the laryngeal, tracheal and esophage	they may be supplied by the thyroid ima artery or the
Venous drainage	Superior, middle and inferior th	hyroid vein
Lymph drainage	Deep cervical and paratracheal	lymph nodes
Nerve supply	Superior or middle cervical sym	pathetic ganglia

#### Physiology

- The parathyroid glands produce and secretes PTH, a peptide hormone, in response to low blood calcium levels.
- \* PTH secretion causes the release of calcium from the bones by stimulating osteoclast, which secrete enzymes that degrade bone and release calcium into the interstitial fluid.
- PTH also inhibits osteoblasts, the cells involved in the bone deposition, thereby sparing blood calcium. PTH causes increased reabsorption of calcium (and magnesium) in the kidney tubules from the urine filtrate.
- In addition, PTH initiates the production of the steroid hormone calcitriol (also known as 1,25dihydroxyvitamin D), which is the active form of vitamin D3, in the kidneys. Calcitriol then stimulates the increased absorption of dietary calcium by the intestines.
- A negative feedback loop regulates the levels of PTH, with rising blood calcium levels inhibiting the further release of PTH.

#### Chapter 17

**Endocrine System** 



## Histology and Embryology

#### 1) Composed of parenchyma and stroma

#### \* Parenchyma

- ✓ Chief cell (principal cell)
  - Are most numerous
  - o Secrete PTH

#### ✓ Oxyphil cell

- Appear at 7 years and increase with age
- o Function is unknown

#### Stroma \*

- ✓ Reticular connective tissue
- √ Fat cell---increase with age

#### 2) Embryology:

- Superior parathyroid gland formed by: 4th pouch
- Inferior parathyroid gland formed by: 3<sup>rd</sup> pouch

#### 3) Clinical notes

- During superficial Parotidectomy, most reliable landmark for facial nerve identification is
   Tympanomastiod suture
- PTH levels obtained during parathyroidectiomy help to guarantee the successful resection of the abnormal gland by demonstrating a return of the PTH levels to normal after the suspected parathyroid adenoma is removed.



#### Pathology



#### Primary hyperparathyroidism

- There is an increase in PTH, increase serum Calcium (Hypercalcemia) and a decrease in phosphate.
- Occur most frequently in postmenopausal women
- Associated with MEN I and MEN IIa
- Causes:
  - ✓ Parathyroid adenoma-----85 to 95% (confined to single gland)
  - ✓ Parathyroid hyperplasia-----5-10% affecting all 4 gland
  - ✓ Parathyroid carcinoma-----1 %
- Symptom includes:

"Painful Bone, Renal Stone, Abdominal Groan and Psychic Moan".

Note: Hypercalcemia is present along with hypercalciuria (increase loss of calcium in the urine)

#### Familial hypocalciuric Hypercalcemia (FHH)

- Increase in PTH and an increase in calcium level (Hypercalcemia)
- It is due to inactivation mutation in the calcium-sensing receptor in parathyroid and kidney. It is
  an autosomal dominant disorder.
- It results in increased in PTH secretion with consequent calcium retention
- In contrast to primary hyperparathyroidism in which urinary calcium is high FHH has low urinary calcium.

#### Secondary Hyperparathyroidism

- Increase in PTH, decrease in Calcium(hypocalcemia) and increase in phosphate.
- Chronic renal failure is by far the most common cause. Vitamin-D conversion by the kidney to biologically active form is impeded.

#### Tertiary Hyperparathyridism

Increase in all three (increase PTH, increase Calcium and increase in Phosphate)

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Chapter 17

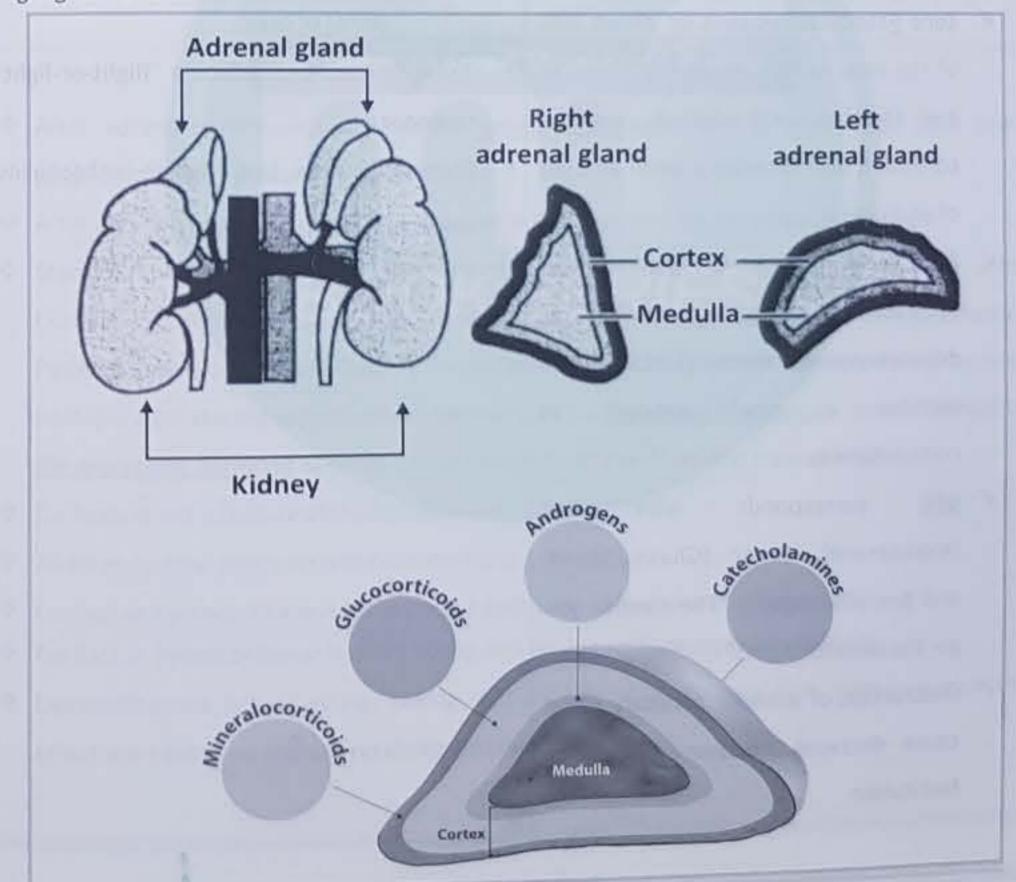
**Endocrine System** 

## Adrenal Gland

#### Anatomy



- The adrenal (or suprarenal) glands are paired endocrine glands situated over the medial aspect
  of the upper poles of each kidney.
- The adrenal glands are located in the posterior abdomen, between the superomedial kidney and the diaphragm. They are retroperitoneal, with parietal peritoneum covering their anterior surface only.
- Separated from the kidney by perirenal or perinephric fat
- The Fetal gland is 1/3rd size of the kidney
- The Right suprarenal gland is pyramidal in shape and left is Crescentric in shape
- · Cortex and medulla have the different embryonic origin
- Pre-ganglionic sympathetic fiber derived from greater splanchnic nerve supply medulla
- Contain nicotinic receptor and having dual nature, acting as an endocrine gland and sympathetic ganglion for SNS



Endocrine System

#### Parts

_	Adrenal Cortex	Adrenal Medulla
	Outer yellowish portionform 80% of	<ul> <li>Inner reddish brown portion———form</li> </ul>
	the adrenal gland	20% of the adrenal gland
٠	Derived from embryonic mesoderm	Derived from ectodermal neural crest cell
٠	Adult zone	Fetal zone
*	The layer of adrenal cortex remember by	<ul> <li>Adrenal medulla is composed of</li> </ul>
	mnemonic GFR:	"chromaffin cell" in anastomosing cords.
	✓ Zona <u>G</u> lomerulosa: Produces and	Cytoplasmic granules contain:
	secretes mineralocorticoids such as	✓ Nor-adrenalin (nor-epinephrine)
	aldosterone.	✓ Adrenalin (Epinephrine) Eighty
	✓ Zona Fasciculate (makes up about 75%	(80%) of cells
	of the total cortex, thickest): Produces	These hormones produce a 'flight-or-fight'
	and secretes corticosteroids such as	response.
	cortisol. It also secretes a small amount	Chromaffin cells also secrete enkephalins
	of androgens.	which function in pain control.
	✓ Zona Reticularis:Produces and	
	secretes androgens such as	
	dehydroepiandrosterone (DHES). It also	
۱	secretes a small amount of	
	corticosteroids.	
	✓ <u>GFR</u> corresponds with Salt	
	(Aldosterone), Sugar (Glucocorticoid)	
	and Sex (Androgen). "The deeper you	
	go, the sweeter it gets".	
	✓ Destruction of anterior pituitary gland	
	cause decrease functioning of zona	
	fasciculate	

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Endocrine System

#### 1) Nerve supply:

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- The adrenal glands are innervated by the coeliac plexus and greater splanchnic nerves.
- Sympathetic innervation to the adrenal medulla is via myelinated pre-synaptic fibres, mainly from the T10 to L1 spinal cord segments.
- End on the nicotinic receptor in the medulla.

#### 2) Blood supply: AIR----

Supplied by <u>numerous arteries</u> (which are branches directly from the aorta) & drained by the <u>single vein</u>

- Aorta
- Inferior phrenic artery
- Renal artery
- . Drained by single vein---renal vein

#### Naseem Sherzad High-Yield Points

- After adrenalectomy, nor-epinephrine remain unchanged due to production from preganglionic, while epinephrine reach to zero
- After adrenalectomy there will be increased in the threshold for salty (Nacl) sensation
- Steroid replacement therapy after adrenalectomy should be reserved for patients with Cushing syndrome (overt or subclinical) and patients undergoing bilateral adrenalectomy. Patients undergoing adrenalectomy for unilateral non-Cushing adrenal tumors do not require postoperative steroid replacement. Aldosterone is a <u>lifesaving hormones</u> hereas cortisol is <u>life protecting hormone</u> because it help to withstand the stress and trauma in life
- Cachexia is not a feature of Hypopituitarism
- All three cortical zones secrete corticosterone
- Cortisol or hydrocortisone is more potent and it has 95% of glucocorticoid activity
- · Cortisol or hydrocortisone is short acting and having sodium retaining potency
- Dexamethasone is long acting, having anti-inflammatory potency and immunosuppressive effect but having no sodium retaining potency

#### Glucocorticoid

Glucocorticoid is C21 steroid, having 21 carbons atom

#### 1) Stimulation of Gluconeogenesis:

- Caused degradation of lipids and protein
- Prevent glucose utilization by tissue

#### 2) Anti-inflammatory and action on blood cells

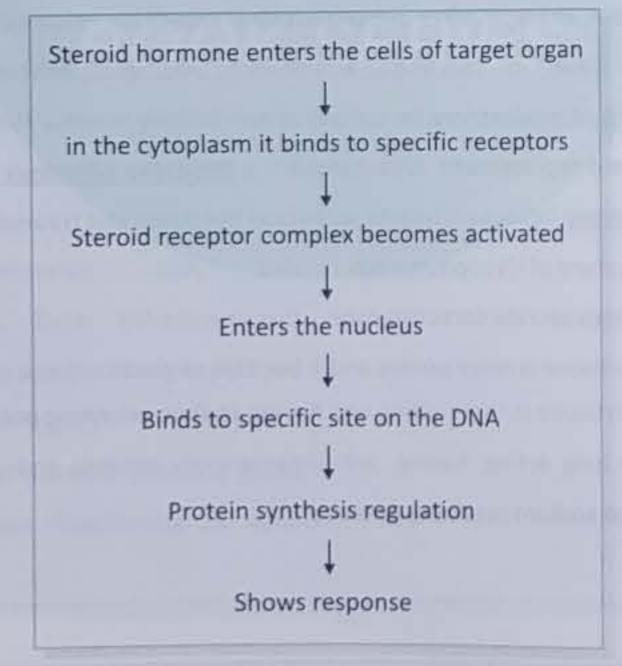
- Inhibit IL-2, decrease the level of eosinophils, basophils and lymphocyte
- Increase the circulation level of neutrophil level, RBC's and platelet
- Inhibit T-lymphocyte proliferation
- Inhibit the release of histamine and serotonin from mast cell

#### 3) Other function:

- Cause up-regulation of alpha—1 receptor in blood vessel—which causes vasoconstriction and increases BP. Also, note that thyroid hormone increase sensitivity of B1 receptor in heart to epinephrine and cause tachycardia
- Cause inhibition of wound contraction
- Inhibit fibroblast-----cause stria
- Inhibit osteoclast and cause osteoporosis and Osteopenia

#### 4) Steroids MOA:

- Gene
- Transcription
- . The Receptor is in the nucleus

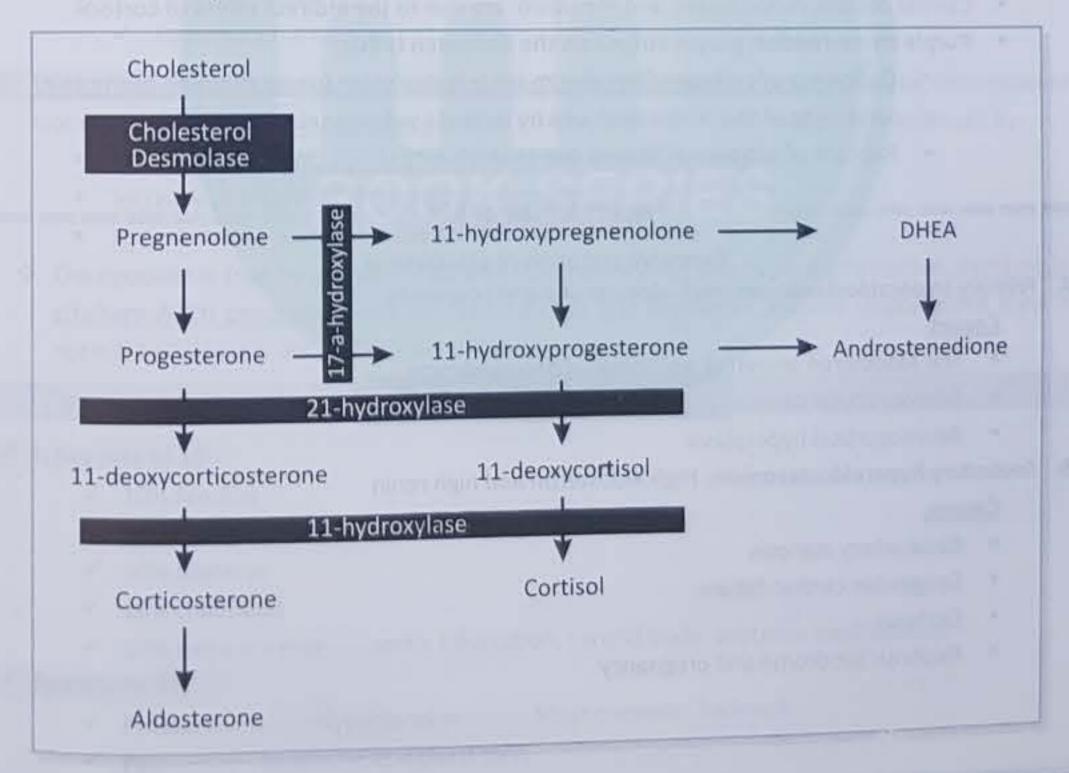


\* overview:

- Adrenocortical Hormone Biosynthesis
- ....
- All adrenocortical hormones, known as Corticosteroids, are steroid hormones.
  - As with all steroid hormones, biosynthesis of corticosteroids is based on sequential enzymatic modification of cholesterol.
  - The three different subtypes of adrenocortical hormones are achieved by different pathways of enzymatic modification, yielding hormones with different chemical side groups. Because each zone of the adrenal cortex expresses a different set of modifying enzymes, different hormones are produced in each zone.
  - 17-ketosteriod in urine maximally seen in normal male

#### Biosynthesis chemistry:

- The overall pathway for adrenocortical hormone biosynthesis is presented in the diagram below.
- Note that cholesterol is the starting material for all the hormones. Each zone of the adrenal cortex possesses only those enzymes necessary to synthesize its particular hormone; thus, no zone possess all of the enzymes shown.
- The only enzyme which is shared by all the zones is Cholesterol Desmolase which is required to activate cholesterol for any further chemical modification.
- Expression of cholesterol desmolase depends on the presence of ACTH a hypothalamic hormone; therefore, in the absence of ACTH no adrenocortical hormones are produced.



#### Hyperfunctioning adrenal gland

There will be hypokalemia, Metabolic alkalosis, hypertension and hypernatremia

#### **Cushing syndrome**

increase in cortisol due to variety of causes

#### \* Causes:

- Exogenous cause: latrogenic Cushing syndrome: This is the most common cause of cushing syndrome and caused by administration of Glucocorticoids
- Endogenous causes:
  - ✓ <u>Cushing disease (70%):</u> Cushing syndrome secondary to the pituitary tumor is called Cushing disease and this is the <u>most common endogenous cause</u>.
  - ✓ Adrenal tumor (15%): adrenal adenoma(most common) and adrenal carcinoma
  - ✓ Ectopic ACTH production (15%): Small cell carcinoma of the lung is the most common cause, other causes include medullary carcinoma of the thyroid and Carcinoid tumors

#### Clinical features:

- Less Most specific: Spontaneous bruising, proximal myopathy and skin striae
- More specific: Central obesity with extremity wasting and moon fascia
- Non-specific: Secondary diabetes, HTN, osteoporosis, Hirsutism, buffalo hump
- · Central obesity, moon facies, and Hirsutism are due to the indirect effect of cortisol
- Purple striae-reddish purple stripes on the abdomen is due:
  - ✓ Deficiency of collagen fiber due to protein depletion (cause thinning of the skin)
  - ✓ Stretching of the abdominal wall by increase subcutaneous fat
  - ✓ Rupture of subdermal tissues due to stretching

#### Hyperaldosteronism

Excessive secretion of aldosterone

A. Primary hyperaldosteronism: High aldosterone and Low renin

#### Causes

- The Aldosteron secreting adenoma—Conn syndrome
- Adrenocortical carcinoma
- Adrenocortical hyperplasia
- B. Secondary hyperaldosteronism: High aldosteron and high renin

#### Causes:

- Renal artery stenosis
- Congestive cardiac failure
- Cirrhosis
- Nephritic syndrome and pregnancy

#### Chapter 17

**Endocrine System** 

## Adrenal insufficiency: Hypofunctioning



- Result from inadequate secretion of Cortisol and Aldosterone
- . Two categories:

#### 1) Primary Adrenal insufficiency:

- Decreased cortisol/Aldosterone associated with <u>Increased ACTH.</u>
- Caused by:
  - ✓ <u>Acute:</u> Waterhouse-Friederichsen Syndrome(due to adrenal hemorrhage)
  - Chronic: Addison's disease (two most common cause is tuberculosis in developing countries and autoimmune adrenalitis in developed countries, HIV, sickle cell disease and metastatic cancer is less common)

#### 2) Secondary Adrenal insufficiency:

- It is the <u>most common</u> cause of Adrenal insufficiency
- Decrease cortisol/and or Aldosterone associated with <u>Decreased ACTH.</u>
- · Cause by:
  - ✓ Rapid withdraw of long term glucocorticoid therapy (most common cause)
  - ✓ Pituitary tumor
  - ✓ Hypothalamic disease
- 3) <u>Clinical pearls:</u> Clinically <u>primary Adrenal insufficiency(Addison's disease)</u> can be differentiated from <u>secondary Adrenal insufficiency</u> is that Primary adrenal insufficiency is characterized by:
  - Skin hyperpigmentation (ACTH contains the MSH fragment)
  - Increase pituitary ACTH production
  - Hyperkalemia and metabolic acidosis
- The opposite is true for secondary adrenal insufficiency: No skin hyperpigmentation, decrease in pituitary ACTH production and no hyperkalemia and metabolic acidosis (Aldosterone level is normal because it is not ACTH dependant).

#### ·...

Pheochromocytoma



#### It has rule of 10

- ✓ 10% familial
- √ 10% malignant----means 90% benign
- ✓ 10% bilateral
- ✓ 10% childhood
- √ 10% extra-adrenal-----aortic bifurcation, carotid body, posterior mediastinum

#### → Symptoms:5P

- ✓ Pressure-------Hypertension------Most common, hallmark
- ✓ Pain----headache and chest pain
- ✓ Palpation----tachycardia, tremor, weight loss, fever

#### ✓ Perspiration——profuse sweating

✓ Pallor

#### Investigation:

- ✓ Increase 24-hour urinary metanephrines(catecholamine metabolites ) --Highest specificity---99.7%
- ✓ Increase Plasma catecholamine—Highest sensitivity——96%
- ✓ CT/MRI first line for localization of adrenal tumor and sympathetic chain tumors
- ✓ MIBG for localization of extra-adrenal tumor and tumor not detected by CT/MRI.

#### Treatment:

- ✓ Laparoscopic adrenalectomy is the treatment of choice for Pheochromocytoma.
- ✓ Both alpha-blocker (phenoxybenzamine and beta-blocker (propranolol) are given
- ✓ Beta-blocked should not be introduced until the patient is alpha blocked.
- ✓ If left untreated lead to death

#### Diabetes Insipidus (DI)

#### Central Diabetes Insipidus (CDI)

- . It is due to the lack of ADH
- An increase in urine osmolality of greater than 50% reliably indicates central diabetes insipidus,
- . It is caused by:
  - ✓ Head trauma
  - ✓ Tumors of hypothalamus
  - ✓ Craniopharyngioma
  - ✓ Inflammation of hypothalamus

#### Nephrogenic Diabetes Insipidus (NDI):

- It is due to unresponsiveness of collecting tubules to ADH
- An increase of less than 10% indicates nephrogenic diabetes insipidus
- Causes
  - ✓ Lithium
  - √ Hypokalemia
  - √ Nephrocalcinosis
  - ✓ Demeclocycline

#### The Differences on the basis of water deprivation test:

#### Stage I

Water deprivation for 0-8 hours

- ✓ If after 8 hours, urine concentrates———Primary polydipsia

#### Stage II

Give desmopressin 1 µg IM

- If urine concentrate after desmopressin------CDI
- If urine does not concentrate after desmopressin-----NDI

## SEX HORMONES

Testosterone and Dihydrotestosterone

# Testosterone is produced by Leydig cell Testosterone cause growth of hair over the pubis, upward along the linea alba sometime to the umbilicus and above, on the face, usually on the chest Less than 1% of the total testosterone in the plasma is derived from DHEA. Endogenous androstenedione is the immediate precursor of testosterone.

- Prolong administration of testosterone in man causes Azoospermia
- Testosterone levels are at their highest during adolescence and early adulthood
- Testosterone levels is lowest during childhood/Pre-school children
- As men get older, their testosterone levels may decline about 1 percent per year after age 30.

#### Actions:

✓ Increase in muscle mass

Shown In MNS figure 1

- ✓ Spermatogenesis of Sertoli cell (paracrine effect)
- ✓ Cause Descend of testis in late fetal life
- ✓ Cessation of the pubertal growth spurt (Epiphyseal closure)
- ✓ Has a powerful anabolic effect in causing greatly increased deposition of protein everywhere in the body but especially in the muscle
- ✓ Growth of the penis and seminal vesicle, increase in the thickness of laryngeal cartilage
- Negative feedback on anterior pituitary
  and Libido
- ✓ Testosterone is metabolized to dihydrotestosterone (by 5-α reductase) and estradiol (by aromatase). Shown In MNS figure

## Dihydrotestosterone More potent than testosterone

#### Actions:

- ✓ Male hair pattern, male pattern baldness
- ✓ Sebaceous gland activity and growth of prostate
- ✓ Secreted by the fetal adrenal cortex
- ✓ Differentiation of penis, scrotum and prostate

#### Androgen insensitivity syndrome (testicular feminizing syndrome)

- ✓ It is caused by the deficiency of androgen receptors in target tissue of male
- ✓ Testosterone Dihydrotestosterone actions in target tissues are absent
- ✓ There are female external genitalia
  and there is no internal genital
  tract
- ✓ Testosterone levels are elevated due to lack of testosterone receptors in the anterior pituitary
- ✓ It is typically characterized by evidence of feminization (i.e., under masculinization) of the external genitalia at birth, abnormal secondary sexual development in puberty, and infertility in individuals with a 46, XY karyotype.
- ✓ The patient is phenotypically female but genotypically male.
- In fetal life or during pregnancy or during intrauterine life, testosterone secretion from testes is stimulated by <u>human</u> <u>chorionic Gonadotrophin</u>, secreted by placenta

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Cholesterol



Endometrial hyperplasia arise from an excess of estrogen which is a per-malignant condition for endometrial carcinoma

Estrogen is said to be associated with an increased risk of the Breast carcinoma.

Estrogen has cardioprotective role (progesterone has no cardioprotective role).

Estrogen decreases the incidence of osteoporosis in women.

Granulosa-Thica cell tumor is the most common ovarian tumor that produces estrogen.

Granulosa produce estrogen

Estrogen decrease cholesterol level while hypothyroidism cause increase in cholesterol level

Negative feedback for testosterone occurs at the hypothalamus; for estrogens, it occurs at the pituitary.

Estrogen containing OCP increase risk of Thromboembolism > Breast cancer

High estrogen containing OCP increase risk of endometrial carcinoma

Low estrogen containing OCP increase the risk of hepatic adenoma

 At the onset of puberty, estrogen plays a role in the development of female secondary sexual characteristics such as breast, wider Hip, pubic hair and armpit hair

· Differences:

Estrone: ✓ Produce after Menopause

✓ Source adipose tissue and adrenals

✓ One woman become Single again

• Estradiol

✓ Non-pregnant reproductive year

✓ Source: follicle (Granulosa), ovary

✓ Most potent estrogen

√ Women is like a Doll

Estriol:

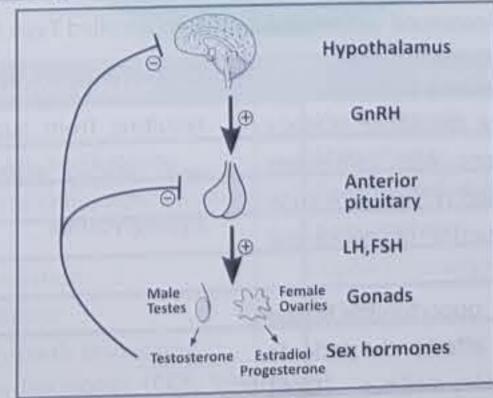
✓ Hormone of Pregnancy

√ Source placenta

✓ Weakest of three estrogens

✓ Mom, dad and baby,---Tri in pregnancy

✓ Used for the triple screening of congenital abnormality



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**AMINOGLUTETHAMIDE** Pregnenolone Progesterone 17a-hydroxylase ABIRATERONE ACETATE 17a-hydroxy 17a-hydroxy [progesterone pregnenolone Estrone --> Androstenedione Dehydroepi-AMINOGLUTETHIMIDE, ANASTROZOLE. androsterone Aromatase LETROZOLE, EXEMESTANE (DHEA) Testosterone Estrogen DUTASTERIDE 5a-reductase FINASTERIDE Dihydroxytestosterone

MNS FIGURE 1

(DHT)

#### Estrogen and Progesterone

Estrogen	Progesterone
Develops duct system	Develop acinar system
<ul> <li>Increase fat deposition</li> </ul>	Block prolactin action on breast
<ul> <li>Increase salt and water retention</li> </ul>	Induce diuresis
<ul> <li>Increase epithelial thickness vascularity</li> <li>Cause vasodilation in spider nevi</li> </ul>	and Decrease epithelial thickness and vascularity
<ul> <li>Feedback inhibition of FSH and LH</li> <li>When estrogen level exceed 200mg it will promote ovulation by indu an LH surge</li> <li>Induce copious and alkaline mu production</li> </ul>	cing production
<ul> <li>Inhibit ovulation</li> </ul>	Inhibit ovulation
<ul> <li>Bone: stimulate osteoblast, contemporaries and protect against osteoporosis</li> <li>Vascular: increase risk</li> <li>Thromboembolism and serum HDL</li> </ul>	Inhibit uterine contraction  Increase has all hody temperature

**Endocrine System** 

NAME AND ADDRESS OF TAXABLE PARTY.

## DIABETES MELLITUS (DM)

#### **Naseem Sherzad High-Yield Points**

- Dry gangrene is most common in DM
- . DM with superimposed infection---wet gangrene
- Diabetic foot is wet gangrenes
- Diagnostic criteria-----albumin in urine or microalbuminuria
- · Cause of ulcer in DM---- angiopathy + neuropathy
- Polyphagia in DM is due to increase in—blood glucose level
- Cause of polyuria in Hypercalcemia is due to---osmotic diuresis
- . Chromium can use for the treatment of DM. Chromium is an insulin cofactor.
- HTN plus DM DOC----ACE inhibitors
- . The most common cause of death is the cardiovascular problem
- Multifactorial involvement seen in DM
- Treatment of diabetes insipidus———desmopressin
- Diabetic patient with gastric upset and bloating best drug----Prokinetic
- . Kimmelstiel-Wilson syndrome is a kidney condition associated with long-standing diabetes. It affects the network of tiny blood vessels (the microvasculature) in the glomerulus, a key structure in the kidney that is composed of capillary blood vessels and which is critically necessary for the filtration of the blood.

Type-I Diabetes Mellitus	Type-II Diabetes Mellitus
HLA DR3 and/or HLA DR4 is associated with increased susceptibility to Type 1 diabetes	<ul> <li>Genetic predisposition relatively strong in Type II DM (90% concordance in identical twins, polygenic)</li> <li>Obesity is the major cause of increased insulin resistance in type-II DM</li> </ul>
Diabetic Ketoacidosis  It is the hallmark of Type 1 diabetes  Characterized by hyperglycemia, hyperketonemia and increased anion gap metabolic acidosis  Kussmaul's breathing—Deep breathing (airhunger) to compensate metabolic acidosis with the odor of acetone. Also, remember Kussmaul's sign—raised JVP on inspiration which is a clinical feature of pericardial tamponade  Mucormycosis is an opportunistic fungal infection that mainly affects the patients	It is a metabolic emergency characteristic of uncontrolled Type-II Diabetes mellitus     Characterized by severe dehydration resulting from sustained osmotic diuresis and urinary fluid loss due to chronic hyperglycemia

Chapter 17

**Endocrine System** 

#### Insulin, Glucagon and C-Peptide

## INSULIN

- Insulin increases the activity of Na\*-K\* ATPase in the cell membrane, so that more K\* is pumped into the cell. MOA of insulin-----tyrosine kinase mechanism
- Insulin inhibits ketoacid formation and insulin deficiency causes Ketoacidosis.
- The net effect of insulin is the storage of CHO, protein and fat and is called the hormone of abundance
- Cause hypokalemia and osteoporosis
- · Somatostatin inhibits insulin by the paracrine way
- · Insulin is the bio-engineered drug approved by FDA
- Insulin secretion is inhibited by beta-blocker
- Insulin does not cross the placenta
- Delayed action of Insulin is Increase in mRNAs for lipogenesis
- Degraded in kidney and liver by enzyme insulinase
- · Oral glucose will cause the release of more insulin
- Effect on carbohydrate metabolism: hypoglycemic effect
  - ✓ Inhibit glycogen breakdown by inhibiting phosphorylase
  - ✓ Promote facilitated diffusion of glucose into cell by activating glucokinase
  - ✓ Promote glucose utilization and Inhibit Gluconeogenesis in liver
  - ✓ Convert excess glucose into fatty acid
- Fat metabolism:
  - ✓ Form fatty acid from the excess of live glucose
  - ✓ Prevent ketogenesis, Decreased lipolysis
- · Protein metabolism:
  - ✓ Inhibit protein catabolism, stimulate protein synthesis,
- On growth:
  - ✓ Insulin function synergistically with growth hormone to promote growth by protein formation
- Overall effects:
  - ✓ Overall, Insulin can be considered the "anabolic" or building hormone

#### Regulation of Insulin

Stimulation Factor	Inhibiting Factors
Hyperglycemia	Hypoglycemia
ructose, Mannose, AA, and ketones	Starvation
Parasympathetic stimulation, Ach	Exercise and stress
Increase blood FFA	Somatostatin
Beta-adrenergic stimulation	Alpha-adrenergic activity
Insulin resistance, obesity	Leptin
Glucagon, Cortisol, Growth Hormones And Gastrointestinal hormones (CCK, Gastrin, secretin)	

NASEEM SHERZAD FCPS -1 HIGH-YIELD

with uncontrolled diabetes mellitus---(DKA)

#### **GLUCAGON**

- Glucagon has a major role in maintenance of normal concentration of glucose in blood, and is often described as having the opposite effect of insulin. That is, glucagon has the effect of increasing blood glucose levels.
- Glucagon marinating blood glucose level by increasing Gluconeogenesis and glycogenolysis (in the liver)
- At the end of the marathon race, the person will be having high glucagon and low insulin in order to prevent hypoglycemia
- Glucagon effect on the heart is like dopamine
- Glucagon, which does not depend on beta receptors for its action, has both Inotropic and chronotropic effects
- Stimulator of glucagon: CCK, gastrin (hypoglycemia increase gastrin level), cortisol, exercise, infection, beta-adrenergic stimulators, hypoglycemia
- Inhibitor of glucagon: Glucose, Somatostatin, secretin, FFA, ketone, insulin, Phenytoin
- Glucagon and catecholamine activate the enzyme glycogen phosphorylase
- Mechanism of action: Glucagon binds to a specific glucagon receptor in the cell membrane, a G Protein Coupled Receptor (GPCR). This activates the enzyme adenylate cyclase which increases cAMP intracellularly. This activates protein kinase A which phosphorylates and activates a number of important enzymes in target cells.

#### C-Peptide

- This test is used to differentiate between type I and type II DM
- The connecting peptide, or C-peptide, is a short 31-amino-acid polypeptide
- Measurement of C-peptide levels together with insulin can differentiate between hypoglycemia due to insulinoma(high C-peptide) and therapeutically administrated insulin (low c-peptide)
- Factitious (or factitial) hypoglycemia may occur secondary to the surreptitious use of insulin. Measuring C-peptide levels will help differentiate a healthy patient from a diabetic one.

#### Glucose utilization by muscles

- During most of the days muscle utilize fatty acids for energy because "resting" muscle membrane is impermeable to glucose
- Muscle can utilize glucose under two condition:
  - ✓ During exercise (without insulin), because "exercising" muscle membrane becomes permeable to glucose
  - ✓ Few hour after meal because insulin is present to promote glucose entry into muscle fibers
- Glucose can be deposited in muscle as " muscle glycogen"
- In healthy man, metabolic requirement may exceed the oxygen supply in skeletal muscle

- -----Brain
- -----Intestine
- -----Cornea
- ----kidney
- ----Liver

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#### Chapter 17

#### **Endocrine System**

- B-----Beta cell
- -----Adipose tissue
- R-----Resting muscle
- · Note:
  - ✓ BR-----Glut-1---first 2 in BRICKL-BAR
  - ✓ ICKLB-----Glut-2
  - ✓ AR-----Glut-4-----last two in BRICKL-BAR
  - ✓ Adipose tissue and resting skeletal muscle ----insulin-dependent intake
  - ✓ Remain all are insulin-independent organ

## WHO Diagnostic Criteria for Diabetes Mellitus

#### CRITERIA 1:

- Symptomatic patient (i.e. polyuria, polydipsia and weight loss) PLUS
- Abnormal venous glucose on ONE occasion I-e
  - √ Fasting blood glucose >126mg/dl
  - √ Random blood glucose >200mg/dl

#### Criteria 2:

- Asymptomatic patient PLUS
- Abnormal venous glucose on TWO occasions I-e
  - ✓ Fasting blood glucose >126mg/dl
  - √ Random blood glucose >200mg/dl

#### Criteria 3:

- " HBAIC of > 6.5%
- It is recently accepted criteria

#### Oral glucose tolerance test:

It is required only for diagnose of

- Borderline cases
- Gestational diabetes
- Those patients having a serum fasting glucose level greater than 110 but less than 126 gm/dl OR oral glucose tolerance test(OGTT) value of greater than 140 but less than 200mg/dl are considered to have impaired glucose tolerance, also known as pre-diabetes. Benedict test is used to detect reducing sugar in the urine

#### HIGH YIELD POINTS

#### 1) Prolactinoma:

- The most common functioning pituitary adenoma is prolactinoma.
- Amenorrhea, galactorrhea, loss of libido and erectile dysfunction are the clinical feature of prolactinoma.
- 2) Growth hormone adenoma is the 2<sup>nd</sup> most common functioning pituitary adenoma.
- 3) The first sign or symptoms of Hypopituitarism secondary to the pituitary tumor is hypogonadism because the hormone which lost first is GnRH followed by loss of GH, TSH and last is ACTH.
- 4) Craniopharyngioma is the most common cause of Hypopituitarism in children.
- 5) The most common intra sellar- tumors are pituitary macroadenoma.
- 6) The most common supra sellar- tumor is Craniopharyngioma
- 7) The most common para-sellar tumors are meningioma.

- The most common tumor of the adrenal medulla in the adult is Pheochromocytoma and the most common tumor of the adrenal medulla in children is Neuroblastoma.
- 9) Chronic Renal failure is by far the most common cause of secondary hyperparathyroidism
- 10) The most common cause of severe Hypercalcemia is Malignancy.
- 11) The Level of Cholesterol is elevated in hypothyroidism. There is pseudohyponatremia in hypothyroidism
- 12) Hashimoto's thyroiditis is also known as chronic lymphocytic thyroiditis
- 13) Silent thyroiditis is also known as subacute lymphocytic thyroiditis or painless thyroiditis
- 14) De Quervain thyroiditis is also known as subacute granulomatous thyroiditis (painful thyroiditisunique feature) .---- non-caseating granuloma
- 15) Non-functioning nodule has the highest chance of malignant transformation
- 16) Latent tetany is seen in Conn's disease
- 17) T4 is 90% and T3 is 10%, T3 is more active than T4, T4 is converted to T3 by iodinase
- 18) Most common site of ectopic thyroid tissue site is the base of the tongue and the most common site of the ectopic salivary gland is mandible followed by gingiva
- 19) Recombinant growth therapy causes benign intracranial hypertension
- 20) Congenital adrenal hyperplasia:
  - Also called adrenogenital syndrome
  - Patient have ambiguous genitalia like the elongated clitoris, 46XX
  - The most common enzymatic defect in congenital adrenal hyperplasia (CAH) is a 21hydroxylase deficiency, which is required for cortisol biosynthesis and accounts for more than 90% of cases.

#### Half-life Half-life of TSH-Half-life of T4-Half-life of T3-----Half-life of ACTH----Half-life of Aldosterone------20 min Half-life of insulin -Half-life of PTH------10 min Half-life of catecholamine-----2 min Half-life of GnRH-----2-4 min Half-life of oxytocin-----3-5 min Half-life of Kanamycin in perilymph -----4 hour Basal Metabolic Rate (BMR)

- . The minimum amount of energy required by the body to maintain life at complete physical and
- mental rest in post-absorptive state \* BMR depends on age, sex, body surface area, activity level and thyroid hormones level
- Hyperthyroid have high BMR, hypothyroid have low BMR
- · Epinephrine, cortisol, sex hormone and growth hormones increase BMR
- . BMR in resting condition is maintained by the liver
- The moderate increase in BMR occur in the exercise

# C H A P T E RBONES & SKIN

## **Bones**

#### Histology

#### - Compact bone:

- Compact bone, which has no trabeculae or bone marrow cavities
- The structural unit of compact bone is the osteon or Haversian system.

#### Haversian system (Osteon):

- · Haversian system are long cylinders that run approximately parallel to the long axis of the diaphysis
- Haversian system is composed of 4-20 concentric ring (lamellae) surrounding a central Haversian canal, which contains blood vessels nerves and loose connective tissue
- They are often surrounded by an amorphous cementing substances
- . They are interconnected by Volkmann canals, which also connect to the Periosteum and endosteum and carry the neurovascular supply

#### Volkmann canal: (Vascular canal)

The canal that runs at the right angle to the central canal and perforates the shaft of the bone

#### Spongy bone:

- Spongy bone contains trabeculae and spicules giving it a honey-comb appearance
- Trabeculae: are irregularly arranged and contain lamella and osteocytes, but contain no osteon, as they receive nutrients from the marrow tissue

#### Bone matrix:

- The inorganic (calcified) portion (65%): is composed mainly of calcium hydroxyapatite, which consists 99% of the body calcium store and 85% of body phosphorus. The inorganic matrix also houses 65% of sodium and magnesium stores
- The organic portion of the bone matrix (about 35% of the dry weight) consists primarily of:
  - √ 95% collagen fibers (type 1 collagen)
  - √ 5% chondroitin sulfate
- If mineral removed------bone is too bendable
- If collagen removed——bone is too brittle

#### Periosteum

- \* The outer covering of each bone is made from fibrous connective tissue called Periosteum
- The Periosteum function to distribute blood vessels to bone
- Sharpey fibers attach the Periosteum to the bone surface
- Layers

#### Inner layer:

O Osteoproginator layer, deposition of bone in the fracture is due to the activity of periosteal layer

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#### o Protect bone and assist In fracture repair

#### ✓ Outer layer

o Dense Fibrous collagenous layer



#### S Osteoproginator cells

- . These spindle-shaped cells are derived from embryonic mesenchyme and are located in the Periosteum and endosteum
- \* They are capable of differentiating into osteoblast. However, a low oxygen tension, they may change into chondrogenic cells

#### Costeoblast:

- Bone forming cell, form bone fiber and matrix
- On the bony surface, they resemble a layer of Cuboidal, basophilic cells as they secret matrix.
- Smaller uninucleated cell
- Involved in the initiation of mineralization
- Synthesis of the organic components of the matrix (collagen type-1, proteoglycan, glycoprotein)
- When synthetically active, they have a well-developed RER and Golgi complex
- Produce new bone through a process called ossification
- Compact bone contain osteoblast cell in the lacuna
- Contain alkaline Phosphatase-----help in CaPO4 deposition
- Estrogen, testosterone and PTH stimulate osteoblastic activity
- Cortisol----inhibit maturation of osteoblast
- Growth hormone----stimulate IGF-1, resulting in osteoblast maturation

#### Osteoclast

- Developed from monocytes or macrophage
- Large multinucleated cell and Their Cytoplasm is acidophilic
- Release mineral through a process of osteolysis
- · At a site of active bone resorption, the osteoclast forms a specialized cell membrane, the "ruffled border" that opposes the surface of the bone tissue.
- Congenital Defective osteoclast function-----OsteoPetrosis
- Osteoclast function in the resorption of bone (osteolysis)
- They form and reside in a depression known as Howship lacuna, which represents the area of bone resorption
- · Contain acidic Phosphatase----which produce lactic acid and Hyaluronic acid
- Osteoclast secret acid, which decalcifies the surface layer of bone and Secret enzyme that digest matrix
- Acid hydrolases, collagenases and other proteolytic enzyme secreted by osteoclast then degrade the organic portion of the bone
- Osteoclast resorb the organic and inorganic residues of the bone matrix and release them into connective tissue capillaries

#### Osteocytes:

- Entrapped osteoblast are known as osteocytes
- Osteocytes communicate with each other via gap junctions on the narrow cytoplasmic

#### Chapter 18

Bones & Skin

## process that extend through canaliculi

- They are mature bone cells that occupy individual lacunae as mature resting bone cell
- They contain abundant heterochromatin, a paucity of RER, and a small Golgi complex
- Most numerous cell
- Cant form collagen
- Stimulated by Calcitonin and inhibited by PTH
- Calcium for bone repair comes from bloodstream

#### **Parts of Young Bone**

#### 1) Epiphysis:

- · A secondary ossification center established in the epiphysis
- · Epiphyseal arteries supply the end of long bone
- \* Types:

#### Traction Epiphysis:

- o Traction epiphysis is non-articular and does not take part in the transmission of weight
- Provide attachment to the tendon of muscles
- Example are tubercle of humerus and trochanters of the femur

#### ✓ Pressure Epiphysis:

- Develops at the articular ends of the long bone,
- These epiphyses take part in the transmission of weight
- E.g. Head of femur, head of the humerus and Lower end of radius etc.

#### ✓ Atavistic Epiphysis:

 These epiphyses are phylogenetically independent but they become fused in man. Examples are the coracoid process of scapula and os trigonum.

#### 2) Diaphysis: middle of long bone

- Diaphysis is the strongest part of the bone
- Primary ossification center: PD-- Diaphysis
- Supplied by nutrient arteries

#### 3) Metaphysis

The ends of diaphysis near the epiphyses are known as metaphyses. Since a long bone has two ends so there are two metaphyses. Each metaphysis is the zone of active growth of a long bone. Before the fusion of diaphysis and epiphyses, the metaphyses are richly supplied with blood through end arteries forming hairpin bends. This is the common site of Osteomyelitis in children.

#### 4) The Epiphyseal plate of cartilage

- This is a plate of cartilage separating epiphyses from metaphyses. The cells of this cartilage plate proliferate and are responsible for the lengthwise growth of a long bone.
- When the age of maturity arrives, this cartilage plate ossifies and then the bone can no longer grow in length.
- In adolescent, through the end of active growth, the epiphyses of the long bone contain hyaline cartilage and form an "Epiphyseal growth palate"
- In the adult, the Epiphyseal plate becomes an "Epiphyseal line"
- This plate of cartilage is nourished by both Epiphyseal and metaphyseal arteries.
- Hypovitaminnosis A-----diminish the thickness of Epiphyseal plate
- Hypervitaminosis A-----accelerates ossification of Epiphyseal plate

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Bones & Skin

#### Types of Ossification

#### 1) Endochondral ossification:

- \* Bones are formed from a cartilage model. A cartilage is formed first and the bone is laid down on it
- . Endochondral bone formation is the process by which long bone are formed. It begins in a segment of hyaline cartilage that serves as a small model for the bone. The two stages of endochondral bone formation involve the development of primary and secondary centers of ossification

#### Primary ossification center:

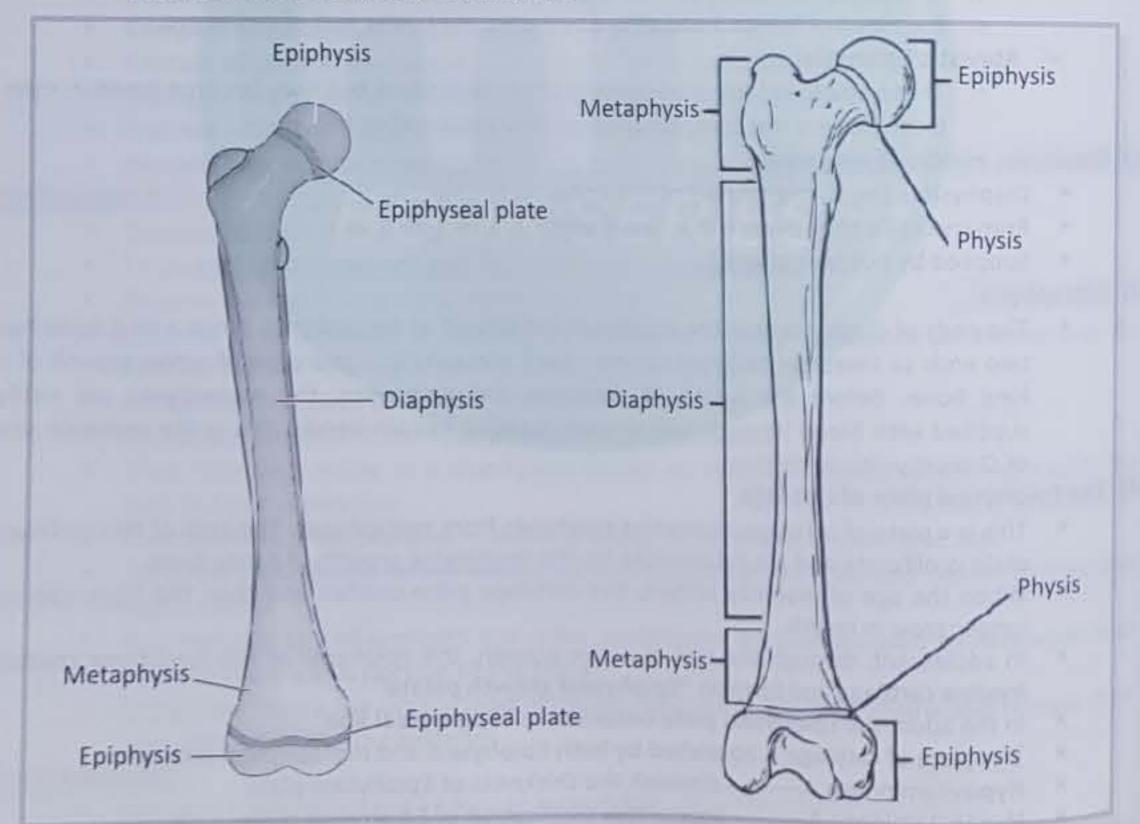
• The primary center of ossification develop at the midriff of the diaphysis of the hyaline cartilage model by the various sequence of events

#### Secondary ossification center:

- · Secondary centers of ossification develops at the epiphysis in a sequence of events similar to that of the primary center, except a bone collar is not formed
- Most secondary ossification centers appear after birth
- · Secondary ossification center at birth present in the distal end of the femur and proximal end of the tibia appears during 34 to 38 weeks

#### 2) Intramembranous ossification:

- . Bone is formed directly on mesenchyme. Dose not form an intermediate cartilage
- Important in the formation of flat bone



## **Pathology**

## **HIGH YIELD POINTS**

- 1) Melon seed bodies are found in joint fluid & are characteristic of tubercular arthritis.
- 2) Giant cell tumor, which effects epiphysis of long bone and shows soap bubble appearance on X-
- 3) Chicken wire calcifications Chondroblastoma
- Osteochondroma is the most common benign tumor of bone

#### 5) Osteomalacia:

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- In Osteomalacia, there is impaired mineralization of the matrix.
- Both hypophosphatemia and hypocalcemia can lead to Osteomalacia.
- · Genetic inactivation of alkaline Phosphatase can also lead to Osteomalacia.
- In Osteomalacia there is the increase in Osteoid maturation time

#### 6) Osteosarcoma:

- The Malignant proliferation of osteoblasts cell
- Code man triangle
- Sunburst pattern or sunray appearance (because of calcification of long vessels)
- Most common in radium watch-dial worker, the most common tumor in the 2<sup>nd</sup> decade
- Associated with strontium-90

#### Osteoid osteoma:

- Benign tumor of osteoblast surrounded by a rim of reactive bone
- · Occur in Teenager,
- Having severe pain around knee and relieved by aspirin

#### **Ankylosing spondylitis**

- Morning stiffness improves with exercise and hot shower.
- Associated with HLA-B27.....Mnemonic PAIR for disease associated with HLA-B27: Psoriasis, Ankylosing spondylitis, Inflammatory bowel disease-related arthritis and Reiter syndrome

#### Investigation:

- ✓ HLA-B27 positive-----but is not a confirmatory test
- ✓ X-ray of sacroiliac joint-----it is the best initial test
- ✓ MRI spine-----it is the most accurate test, it detects abnormalities years before the X-ray becomes abnormal
- ✓ X-ray of spine: "Bamboo spine" i.e. the fusion of vertebra

#### Extraocular features :

- ✓ Anterior uvities-----most common
- Aortic regurgitation and AV block
- Amyloidosis
- Atypical upper lobe pulmonary fibrosis

#### Osteoporosis

- Under optimal conditions, once bone remodeling is completed in a specific area, the resorption spaces are completely filled with new bone. However, after menopause in women, and with aging in men and women, the remodeling cycle becomes unbalanced, and bone resorption increases more than formation does, resulting in net bone loss. The majority of treatments for osteoporosis act to inhibit bone resorption rather than to increase bone formation.
- Calcium/organic matrix ratio normal but the overall mass of the bone is reduced
- Normal bone mineralization and normal lab value in osteoporosis
- Rate of resorption > rate of bone formation, osteoclast more active then osteoblast
- The most common cause of multiple fractures in adult
- Cardinal clues: "bone in bone" appearance, extra dense bone, neural foramen stenosis etc

#### Causes:

- ✓ Old age
- Cushing disease
- COPD and asthma
- Malabsorption and prolong use of PPI's
- ✓ Smoking
- Hypogonadism
- Estrogen deficiency
- ✓ Hyperthyroidism (low testosterone level)
- Diagnosed by: BMD test is called Dual-energy X-ray absorptiometry or DXA test (this is the investigation of choice). BMD provides a measurement called a T-score

#### T-score

- ✓ Normal higher than----: -1
- Osteopenia----: Between -1 and -2.5
- Osteoporosis ----: -2.5 or lower

#### **Naseem Sherzad High-Yield Points**

- Inadequate Mineralization of growing bone———Osteomalacia/Rickets
- Low bone mineral content-----Osteoporosis
- High bone mineral content——OsteoPetrosis
- High bone turn over————Paget disease and hyperthyroidism
- ❖ Low bone turn over——————————Adynamic disease
- In osteoporosis, there is decreased bone mass with a normal ratio of mineral to the matrix.
- In Osteomalacia, the ratio of mineral to the matrix is decreased (i.e. there is too much matrix relative to the amount of bone)
- Osteomalacia, when it appears in children is called rickets
- Osteopetrosis, literally "stone bone", also known as marble bone disease

Bones & Skin

## Paget's Disease

- The synonym for Paget's disease is osteitis deformans.
- Mosaic pattern

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A ....

- . Lion like face and
- Chalkstic fracture
- Diagnose by: 1) isolated increase in ALP (means remain everything is normal like PTH, Ca and phosphate) 2) X-ray finding, 3) urinary marker: Hydroxyproline
- Treatment: The treatment of choice for management of Paget's disease is a bisphosphonate.

#### **Gout & Pseudogout**



#### Gout:

- Gout is a disorder that is related to excess production and deposition of uric acid crystals. Uric acid is the byproduct of purine nucleotide catabolism.
- Monosodium urate deposition
- . The most common site is Podagra, which is the inflammation of the First Metatarsophalangeal joint.
- · Tophi: Aggregates of gouty crystal and giant cell secondary to chronic gout, which is Pathognomonic hallmark of Gout.
- Two differences:

  - ✓ In Lesch-Nyhan disease-----lack of HGPRT
- Investigation:
  - ✓ Joint fluid aspiration: Negatively birefringent and crystal are Needle shape
  - √ X-ray: "Rat Bite" appearance
- Treatment:
  - Acute Gout: First choice is NSAID (indomethacin), local pack and Colchicine
  - Long term treatment: DOC: Allopurinol------MOA-----Xanthine oxidase inhibitor

#### Pseudogout:

- Also known as calcium pyrophosphate deposition disease(CPPD)
- Positively birefringent and crystal are Rhomboid shape.
- The Most common site is knee joint

#### Osteoarthritis



- Bone eburnation
- Loose body (joint mice)
- Osteophytes
- Subchondral cyst formation
- Heberden's node(dip)-----H-DIP
- Bouchard's node (pip)-----B-PIP
- ESR and CRP are normal
- Large joint are affected first
- Pain relieve by rest

#### **Rheumatoid Arthritis**

- Pannus formation(it is granulation tissue formed within synovial tissue)
- Increased vascularity,
- Swan neck deformity,
- Boutonniere or button-hole deformity
- Baker's cyst in the popliteal fossa
- ESR and CRP are raised
- Small joints are affected first.
- Morning stiffness improve by activity (means pain relive by activity)

#### b....

#### **Ewing Sarcoma**

- Malignant, small, Round Blue Cell Tumor, derived from Neuroectoderm.
- 2<sup>nd</sup> most common malignancy in children
- 85% due to translocation of chromosome between 11 and 22
- Increase ESR, fever, anemia, lymphocytosis
- " "onion skin appearance" or "Moth-eaten appearance" on X-Ray occur due to periosteal reaction
- Effect the diaphysis (shaft) of the bone and arise from the endothelial cell.

## **....**

#### Osteogenesis Imperfecta (OI)



- Osteogenesis imperfecta (OI), also known as brittle bone disease, represent a spectrum of conditions linked by qualitative and/or quantitative malfunction of collagen production
- It results in bones that break easily.
- The severity may be mild to severe.
- The underlying mechanism is usually a problem with connective tissue due to a lack of type I collagen. This occurs in more than 90% of cases due to mutations in the COL1A1 or COL1A2 genes These genetic problems are often inherited from a person's parents in an autosomal dominant manner or occur via a new mutation.
- . There are eight types, with type I being the least severe and type II the most severe.
- Diagnosis is often based on symptoms and may be confirmed by collagen or DNA testing.

#### Symptoms:

- ✓ Blue sclera
- ✓ Short height,
- ✓ Loose joints,
- ✓ Hearing loss,
- ✓ Breathing problems and problems with the teeth
- ✓ Complications may include cervical artery dissection and aortic dissection.

Chapter 18

#### Bones & Skin

## Systemic Lupus Erythematosus (SLE)

## Epidemiology:

- ✓ It is the most common connective tissue disease
- ✓ In 90% of cases, the affected individuals are women
- √ Age: 20-30 years

#### Environmental factors:

- ✓ Epstein-Barr virus
- ✓ Ultraviolet light
- ✓ Estrogen
- ✓ Drugs

#### Pathogenesis:

- ✓ The Genetic link appears to be located on chromosome 6
- ✓ High rate of incidence in the monozygotic twins
- ✓ It is due to B and T-cell dysfunction

#### Clinical features:

- ✓ Joint involvement is the most common clinical feature--- >90%
- ✓ Classic butterfly rash with sparing of Nasolabial fold
- ✓ Cardiac features----most common is pericarditis
- ✓ Pulmonary features----most common is recurrent pleurisy and pleural effusion
- Hematologic-----hemolytic anemia, leucopenia and thrombocytopenia. The pathogenesis of thrombocytopenia in SLE patients is heterogeneous, but the most common mechanism is believed to be increased platelet clearance mediated by anti-platelet autoantibodies, which is analogous to the mechanism seen in patients with idiopathic thrombocytopenic purpura
- Renal----it is one of the main determinants of prognosis, the typical lesion is proliferative glomerulonephritis

#### Investigation:

- ✓ Decrease complement level (C3, C4)
- ✓ ANA-----Best screening test
- ✓ Anti-dsDNA----very specific for SLE
- ✓ Anti-Ro antibody: cross the placenta and can cause congenital complete heart block

#### Drug-induced SLE: PPH-IQ

Appears during therapy and commonly anti-Histone antibody Positive

- ✓ Phenytion
- ✓ Procainamide
- ✓ Hydralazine
- ✓ Isonizaed and Quinidine

Bones & Skin

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#### **Systemic Sclerosis**

- Scleroderma: the presence of tight, thickened skin
- Systemic sclerosis: scleroderma plus internal organ involvement
- Renal involvement: it is one of the main causes of death presenting as hypertensive renal crises also called scleroderma renal crises.

#### ₩ Limited scleroderma: Good prognosis

- . It is present in 70% of cases
- The skin hardening and tightening is limited usually just to the fingers and sometimes the hands, forearms or the face. Pulmonary hypertension >> pulmonary fibrosis
- Internal organ damage is less likely in the limited scleroderma type.
- In general, patients with limited scleroderma have a normal life expectancy. Some have
  problems with their GI tract, especially heartburn; severe Raynaud's and musculoskeletal
  pain; and a small subset can develop pulmonary hypertension that can be life-threatening.
- A subtype of limited scleroderma is also known as CREST syndrome.
  - ✓ Calcinosis: calcium deposits under the skin and sometimes in tissues.
  - Raynaud's phenomenon: an exaggerated response to ambient temperatures making the skin of the fingers or toes cold, numb or tingling with color changes.
  - ✓ Esophageal dysmotility: which causes heartburn.
  - ✓ Sclerodactyly: the skin on the fingers becomes thick.
  - ✓ Telangiectasias: enlarged blood vessels that appear as red spots on the fingers, face or other parts of the body.

#### Diffuse scleroderma: Poor prognosis

- It is present in 30% of cases
- Diffuse scleroderma is a subtype of scleroderma where excess collagen production causes skin thickening over large areas of the body, usually the fingers, hands, arms, anterior trunk, legs and face.
- There can be significant associated organ damage, including the gastrointestinal tract, kidneys, lungs and heart. Pulmonary fibrosis >> Pulmonary hypertension
- The tightening of the skin is often associated with dryness and itching.

## = Investigations:

## Sjogren Syndrome

- ANA positive, RF positive
- Anti-RO (anti-SS-A) positive, Anti-la (anti-SS-B)
- · Schirmer test: filer paper in Palpebral fissure to asses tear production
- Rose-Bengal staining: dye that reveals devitalized epithelium of cornea & conjunctiva
- Biopsy: Biopsy of lip (Labial salivary gland biopsy) or parotid gland is the most accurate test. biopsy shows lymphocytic infiltration

#### Treatment:

- Ocular-----artificial tear, cyclosporine eye drops
- · Oral----sugar-free gums, lemon drops, saliva substitute and hydration
- Systemic—NSAIDs, steroid and DMARDS
- Evaluate for lymphoma—because there is 40 fold increase risk of lymphoma

#### Chapter 18

Bones & Skin

## V....

## **TUMORS OF BONES**

#### (1) Bone forming tumors:

#### a) Benign:

- Osteoma (facial bones, associated with Gardner syndrome)
- Osteoid osteoma (young adults usually males, arises in cortex of long bones e.g. femur and pain resolves with aspirin
- Osteoblastoma (larger than Osteoid osteoma, arises in vertebrae and pain doesn't resolve with aspirin)

#### b) Malignant:

 Osteosarcoma (teenagers, arises in the region of the knee, sun burst appearance on x-ray and lifting of Periosteum called Codman triangle, grossly it is white tan, gritty with hemorrhagic or cystic appearance. Biopsy shows large, hyperchromatic pleomorphic cells

#### 2) Cartilage forming tumors:

They occur in the medulla of bones. Benign tumors occur in small bones while malignant tumors occur central bones e.g. pelvic bones.

#### a) Benign:

- Osteochondroma
- Chondroma (x-ray shows O-ring sign )
- · Chondroblastoma

#### b) Malignant:

Chondrosarcoma (it has two types; clear cell Chondrosarcoma and mesenchymal Chondrosarcoma)

#### 3) Miscellaneous: it includes:

- Giant cell tumor (benign, young adults and only tumor to arise in the epiphysis. Arises in long bones in the region of the knee, soap bubble appearance on x-ray. Microscopically it has osteoclastic type multinucleated giant cells and stromal cells)
- Ewing sarcoma (malignant, neuroectodermal in origin, diaphysis of long bones, usually in male children. on x-ray it shows onion skin like appearance. Biopsy shows small, round blue cells that resemble lymphocytes, homer Wright rosettes, tumor cells arranged in a circle with a central fibrillary space.

#### 4) Metastatic tumors:

- More common than primary tumors
- Usually presents as punched out lesions (osteolytic) with exception to Prostatic carcinoma (osteoblastic lesions).
- The most common site is the vertebral column.

## Bone Tumors According to the Site -----Mnemonic: GEOMED

Tumor	Site	Special Feature
Giant cell tumor/osteoclastoma	Epiphysis	Soap bubble appearance on x-ray
Osteosarcoma	Metaphysis	Sun-burst/Codman triangle on x-ray
Ewing sarcoma	Diaphysis	Onion peel appearance on x-ray
Osteoblastoma	Vertebra	

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NASEEM SHERZAD FCPS - 1 HIGH-YIELD

#### SKIN

#### Histology

- The skin is one of the largest organs in the human body, in terms of both its overall size and weight. In an adult male, the skin weighs between 6 and 10 kg (~13 and 22 lbs).
- The average adult skin surface area is 1.5 to 2.0 square meters, in contrast to that of a newborn, whose skin surface area is only 0.2 to 0.3 square meters.
- Waterproofing of skin is determined by the presence of keratin
- Keratinocytes make up approximately 90% of the epidermis

#### Three layers

#### 1. Epidermis

#### Boy Say Girls Look Cute

- Stratum Basale---3M
  - Mitosis
  - Contains:
    - ✓ Melanocytes
    - ✓ Merkel cell—modified free nerve ending
- Stratum Spinosum, contain
  - Langerhans cells---contain Birbeck granules
  - Intercellular bridge (spin desmosome) is characteristic
  - Contain lamellar bodies
  - Acanthosis target this layer
- Stratum Granulosum
  - Most superficial in which nuclei is still present
  - Unmyelinated free nerve ending
  - Contain keratohyalin granules
- Stratum Lucidum:
  - Lack nuclei and granules
- Stratum Corneum

#### Chapter 18

Bones & Skin

- This is the most superficial layer
- Prevent the insensible loss of water because it contains cholesterol filled space
- Contain soft keratin which having no nuclei,
- keratin is responsible for the elasticity of corneal layer of skin

#### 2. Dermis:

- It constitutes 95% of the skin, and 15-40 times thicker than the epidermis
- Contain mast cell

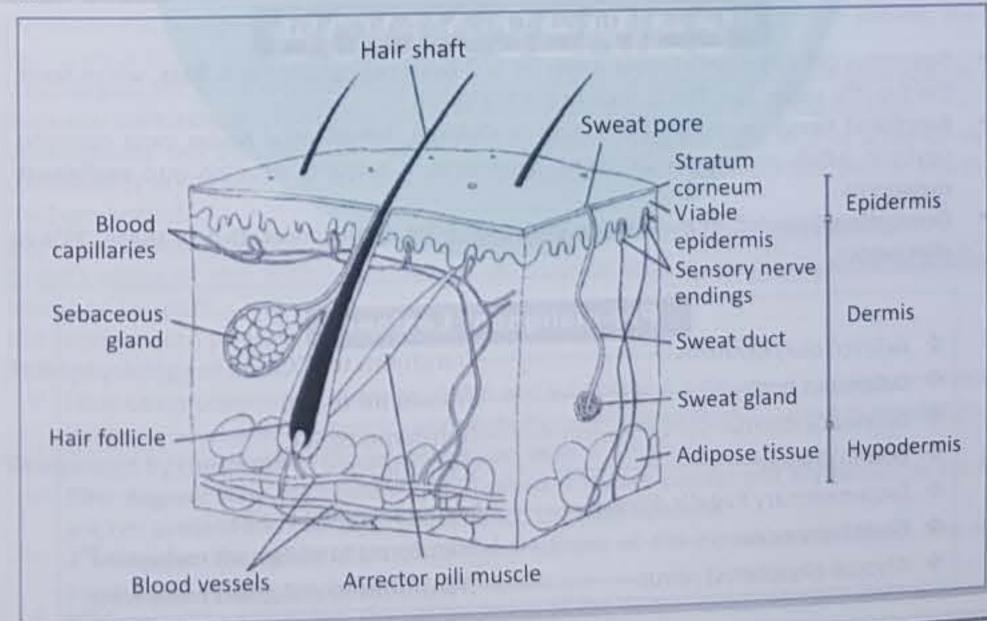
#### Papillary layer

- Areolar connective tissue
- 20%
- Form dermal papilla where Meissner corpuscle present (pain and touch receptor)

#### Reticular layer

- 80%
- Dense irregular connective tissue
- Contain arteries, vein and lymphatics
- Contain sweat gland
- Hold water---hydration
- Contain elastic fiber interlinked collagen fiber
- Contain Krause end bulb, Pacinian corpuscle and rich in loose connective tissue

#### 3. Hypodermis



#### **Pathology**

#### Basal Cell Carcinoma (BCC)

#### BRP

- It is the most common skin malignancy
- > It is also known as "Rodent Ulcer" With Peripheral Palisading
- The ulcer has Raised and Beaded edges.
- > Ultraviolet radiation: it is the most important Risk factor/strongest predisposing factor
- > Over 90% occur on the face above a line from the lobe of ear to the corner of mouth.
- > The most common presentation is as an ulcer that never heals.
- > BCS is locally aggressive and very rarely metastasis by blood but never metastasis through lymphatics
- BCC metastasis is extremely rare

#### **Squamous Cell Carcinoma**

- > It is the second most common skin malignancy.
- > Squamous cell carcinoma arising from a scar known as a "Marjolin's scar"
- > There is usually an ulcerative or cauliflower-like proliferative lesion with an everted edge.
- > SCC spread by all three-method i-e local invasion, lymphatic spread and blood-borne metastasis.
- > SCC is strongly associated with chronic inflammation, chronic sinus trace and pre-existing scar
- > Treatment: Surgical excision

#### Naseem Sherzad High-Yield Points

- Squamous cell carcinoma favour lower lip and Basal cell carcinoma is Boss, which favor the top (the upper lip). This is opposite in the eyelid
- Junctional nevus most common nevus in children, Intradermal nevus most common nevus in adult and dysplastic nevus syndrome in majority develop into malignant melanoma
- Occupational cancer, in general, accounts for 1-5% of all cancer. Out of these, 75% is skin cancer.

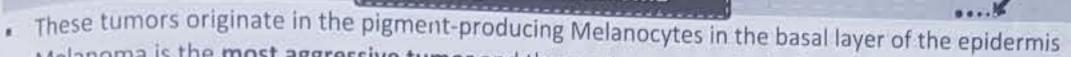
#### **Pre-malignant Lesions**

- Actinic(solar) keratosis-----Transforms to SCC
- ❖ Cutaneous horn—————Transforms to SCC
- ❖ Keratoacanthoma————Transforms to SCC
- & Bowen disease-----SCC in situ
- \* Extramammary Paget's disease-----Adenocarcinoma in situ
- ❖ Giant hairy nevus———————Transforms to malignant melanoma
- Atypical (Dysplastic) nevus————Transforms to malignant melanoma

## Chapter 18

#### Bones & Skin

## Malignant Melanoma



- Melanoma is the most aggressive tumor and the most common site is the hard plate.
- Melanoma at the epidermal site most commonly undergo malignant transformation
- Vertical growth phase have increased metastatic potential
- The tissue biopsy of malignant melanoma contain NK
- NKC are present earlier in chronological order
- Uveal malignant melanoma, orbital extension probably occurs through the emissary's vein, although aggressive tumors may reach the orbit by direct scleral invasion or through optic nerve head.
- Tumor marker S-100B
- Risk factors:
  - ✓ Sunlight is the most important risk factors
  - ✓ UV radiation and Xeroderma Pigmentosa
- There are four types of skin melanoma
  - ✓ Superficial spreading melanoma is the most common type. It is more commonly found on the arms, legs, chest and back.
  - ✓ Nodular melanoma is the second most common type.
  - Lentigo maligna melanoma is less common. ...
  - Acral lentiginous melanoma is the rarest type. The most common site is the plantar surface of the foot (sole of the foot)

Burns



- The second leading cause of death in children. The most common organ affected is the skin.
- Ringer lactate is the fluid of choice for the extensive burn patient
- Pseudomonas aeruginosa are the most common source of infection in burn patient, the initial colonization of a burn is also by pseudomonas
- Candida albicans is the most common non-bacterial infection non-Protozoal in burn patient
- Burn scar contracture is the tightening of the skin after a second or third-degree burn
- Burn patients can also have an important reduction in albumin level due to a higher vascular permeability in the burn wounds that produces exudation with an important protein loss through the burn wound.
- Burn cause massive release of Intracellular potassium and thus cause hyperkalemia
- In burn needs of skin graft is decided on skin appendages, if present no need of graft and if absent go for graft
- I/M Ketamine can be given in burn patient
- Pathophysiology of burn:
  - ✓ Heat cause coagulation necrosis of skin and subcutaneous tissue----release of vasoactive amines -----altered capillary permeability -----loss of fluid-----sever Hypovolemia
- Categorized by the depth of tissue destruction into:
  - ✓ First degree: Only the epidermis is involved. They are painful and erythematous but blister are not present and capillary refill is intact. Look like sunburn
  - ✓ 2<sup>nd</sup> degree: The epidermis and partial thickness of the dermis are involved. The area is
  - ✓ 3<sup>rd</sup>degree: The epidermis, the full thickness of the dermis and potentially deeper tissues are involved. The areas are painless, white and charred

#### **Important Association**

- Erythema nodosum associated with group A streptococcal Pharyngitis
- Erythema marginatum associated with acute rheumatic fever
- Erythema toxicum neonatorum is a common rash in neonates. It appears in up to half of newborns carried to term, usually between day 2-5 after birth; it does not occur outside the neonatal period.
- · Erythema multiform associated with the viral infection and drug reaction
- Erythema migrans associated with Lyme disease
- Pemphigus vulgaris: it is an autoimmune disease caused by antibodies(igG antibodies) directed
  against both desmoglein 1 and desmoglein 3 present in desmosomes. It is classified as a type II
  hypersensitivity reaction
- Most common porphyria is -----porphyria Cutanea Tarda

#### Types of Ulcer

Ulcer refers to the discontinuity of an epithelial surface

The ulcer may characteristic shapes of edge that helps to determine the etiology, e.g.

- · Painful ulcer In the lower leg associated with diastolic hypertension----Martorell's ulcer
- Type of ulcer in basal cell carcinoma------Rodent ulcer (raised and beaded edges)
- The Ulcerative lesion in Squamous cell carcinoma have------Everted edges
- . The Earliest manifestation of Crohn's disease is------Aphthus ulcer
- The Ulcer that may develop in burn patient———Marjolin's ulcer
- Painless indurated ulcer——————————Syphilis

- Intestinal Tuberculosis------Transverse ulcer in the colon
- A venous ulcer is typically shallow with irregular sloping edges whereas an arterial ulcer can be
  deep and has a 'punched out' appearance.

#### Discharge from the Ulcer

- Serous discharge----------------Healing ulcer
- ❖ Purulent discharge————————Spreading ulcer
- Discharge with bony spicule——Osteomyelitis
- Greenish discharge—————————Pseudomonas

## Lichen planus

- Chronic inflammatory disease of the skin, mucous membrane (the mucosal form affects the lining of GIT) and nails
- . It is related to hepatitis C
- The Erosive type has the most common pre-malignant potential
- \* Risk of lichen planus into malignancy occurs in 10-15 years
- Lichen planus rate of conversion into malignancy is 1-10%

# PATHOLOGY

VERAL 19

## Cell injury, Cell death & Adaptation

Reversible Cell injury	Irreversible Cell Injury	
Cellular swellingdue to entry of water to ECF, First manifestation of almost all form of injury to cells	Cell shrinking	
Fatty changes	Amorphous/flocculent densities in mitochondria	
Calcium efflux	Calcium influx	
Decrease Ph and ATP	Severe membrane damage	
Myelin figure	Start with Lysosomal rupture and enzyme release	
Cellular blebs	Karyolysis	
Decrease glycogen	Cytoplasmic contraction band	

Features	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → Karyolysis	Fragmentation into nucleosome-size fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of the cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Invariably pathologic (the culmination of irreversible cell injury)	Often physiologic, means of eliminating unwanted cells; maybe pathologic after some forms of cell injury, especially DNA damage

Nuclear changes: show one of the three patterns, all due to non-specific breakdown

- Karyolysis:-----Basophilia of the chromatin may fade
- Karyorrhexis ------Fragmentation of the nucleus,
- Pyknosis-----Characterized by cell shrinking and increased basophile, here the DNA apparently condenses into a solid, shrunken basophilic mass

#### Fat necrosis:

- Traumatic fat necrosis:
  - This is the most common cause of fat necrosis
  - Example: trauma to human breast
- Enzymatic fat necrosis:
  - ✓ Example: Acute pancreatitis and Omental necrosis

#### Coagulative necrosis:

- There is the preservation of the outline of coagulates cell for a span of some days
- Characteristic of hypoxic death of cells in all tissue except brain
- Calcium is highest in those cells that have undergone Coagulative necrosis

#### 3) Liquefactive necrosis:

Liquefactive necrosis is seen in focal bacterial or, occasionally, fungal infections, because microbes stimulate the accumulation of inflammatory cells and the enzymes of leukocytes digest ("liquefy") the tissue

#### Gangrene:

- Dry gangrene
  - ✓ No infection, bacteria fail to survive
  - ✓ Site: Commonly limbs, e.g. DM
  - ✓ Mechanism: Arterial occlusion
  - ✓ Organ dry, shrunken and black

#### Wet gangrene:

- ✓ Superimposed infection on necrosis, numerous bacteria present
- ✓ Site: More commonly in the bowel, e.g. SMA
- ✓ Mechanism: Blockage of both venous drainage and arterial obstructions
- ✓ Part moist, soft, swollen, rotten and dark

#### Caseous necrosis:

- Caseous necrosis is encountered most often in foci of Tuberculous infection
- Numerous epithelioid cell surrounded by lymphocyte

**Apoptosis** 

**General Pathology** 

#### 1) Apoptosis in Physiologic Situations:

- Death by apoptosis is a normal phenomenon that serves to eliminate cells that are no longer needed and to maintain a steady number of various cell populations in tissue. It is important in the following physiologic situations:
  - ✓ The programmed destruction of cells during embryogenesis, including implantation, organogenesis, developmental involution, and metamorphosis
  - ✓ Apoptosis is a generic term for this pattern of cell death, regardless of the context, but it is often used interchangeably with "programmed cell death.
  - ✓ "Involution of hormone-dependent tissues upon hormone deprivation, such as endometrial cell breakdown during the menstrual cycle, and regression of the lactating breast after weaning
  - ✓ Elimination of potentially harmful self-reactive lymphocytes, either before or after they have completed their maturation, in order to prevent reactions against one's own tissues Cell death induced by Cytotoxic T lymphocytes, a defense mechanism against viruses and tumors that serves to kill and eliminate virus-infected and Neoplastic cells, prevent overcrowding of cell by destroying the mutant cell

#### 2) Apoptosis in Pathologic Conditions

- Apoptosis eliminates cells that are genetically altered or injured beyond repair without eliciting a severe host reaction, thus keeping the damage as contained as possible. Death by apoptosis is responsible for the loss of cells in a variety of pathologic states:
- DNA damage: Radiation, cytotoxic anticancer drugs, extremes of temperature, and even hypoxia can damage DNA, either directly or via the production of free radicals. If repair mechanisms cannot cope with the injury, the cell triggers intrinsic mechanisms that induce apoptosis. In these situations, elimination of the cell may be a better alternative than risking mutations in the damaged DNA, which may progress to malignant transformation.
- Inducing apoptosis of cancer cells is a desired effect of chemotherapeutic agents, many of which work by damaging DNA.
- Cell injury in certain infections, particularly viral infections, in which loss of infected cells is largely due to apoptotic death that may be induced by the virus (as in adenovirus and human immunodeficiency virus infections) or by the host immune response (as in viral hepatitis)
- Pathologic atrophy in parenchymal organs after duct obstruction, such as occurs in the pancreas, parotid gland, and kidney

#### 3) Mechanisms of Apoptosis

- The fundamental or initial event in apoptosis is the activation of enzymes called caspase
- The Central organ in apoptosis is mitochondria
- Two distinct pathways converge on caspase activation, called the mitochondrial pathway and the death receptor pathway. Although these pathways can interact, they are generally induced under different conditions, involve different molecules, and serve distinct roles in physiology and disease
- In H&E-stained tissue of the nuclei of apoptotic cells shows various stages of chromatin and aggregation and ultimately, Karyorrhexis

#### 4) Important difference:

Gene promoting apoptosis: BAX, BAK and Bim

- Initiator caspase-----8-9
- Executioner caspase-----3-6

#### Example of Apoptosis:

#### **Growth Factor Deprivation:**

Hormone-sensitive cells deprived of the relevant hormone, lymphocytes that are not stimulated by antigens and cytokines, and neurons deprived of nerve growth factor die by apoptosis. In all these situations, apoptosis is triggered by the mitochondrial pathway and is attributable to the activation of pro-apoptotic members of the Bcl-2 family and decreased synthesis of Bcl-2 and Bcl-x1.

#### DNA Damage:

Exposure of cells to radiation or chemotherapeutic agents induces DNA damage. and if this is too severe to be repaired it triggers apoptotic death.

#### Accumulation of Misfolded Proteins:

During normal protein synthesis, chaperones in the ER control the proper folding of newly synthesized proteins, and misfolded polypeptides are ubiquitinated and targeted for proteolysis. If, however, unfolded or misfolded proteins accumulate in the ER because of inherited mutations or stresses, they induce "ER stress" that triggers a number of cellular responses, collectively called the unfolded protein response. This response activates signaling pathways that increase the production of chaperones and retard protein translation, thus reducing the levels of misfolded proteins in the cell. However, if this response is unable to cope with the accumulation of misfolded proteins, the result is the activation of caspases that lead to apoptosis.

#### Apoptosis of Self-Reactive Lymphocytes

- Lymphocytes capable of recognizing self-antigens are normally produced in all individuals. If these lymphocytes encounter self-antigens, the cells die by apoptosis.
- ✓ The failure of apoptosis of self-reactive lymphocytes is one of the causes of autoimmune diseases.

#### Cytotoxic T Lymphocyte-Mediated Apoptosis:

Cytotoxic T lymphocytes (CTLs) recognize foreign antigens presented on the surface of infected host cells and tumor cells

#### Intracellular Accumulation

- Pigments are colored substances that are either exogenous, coming from outside the body, or endogenous, synthesized within the body itself.
- The most common exogenous pigment is carbon (an example is coal dust), a ubiquitous air pollutant of urban life
- Endogenous pigments include lipofuscin, melanin, and certain derivatives of hemoglobin
- Lipofuscin, or "wear-and-tear pigment," is an insoluble brownish-yellow granular intracellular material that accumulates in a variety of tissues (particularly the heart, liver, and brain) as a function of age or atrophy.

## **Cellular Adaptation**



**General Pathology** 

#### Hyperplasia:

- Increase in size and number of cell that's why occur in a cell with rapid mitosis
- Hyperplasia is an adaptive response in cells capable of replication, whereas hypertrophy occurs when cells are incapable of dividing
- · Hypertrophy and hyperplasia can also occur together, and obviously, both result in an enlarged (hypertrophic) organ
- Vocal nodule most likely represent hyperplasia and least likely represent atrophy
- Hyperplasia can be physiologic or pathologic.
- . The two types of physiologic hyperplasia are:
  - ✓ Hormonal hyperplasia, exemplified by the proliferation of the glandular epithelium of the female breast at puberty and during pregnancy
  - ✓ Compensatory hyperplasia, that is, hyperplasia that occurs when a portion of the tissue is removed or diseased. For example, when a liver is partially Resected, mitotic activity in the remaining cells begins as early as 12 hours later, eventually restoring the liver to its normal weight.
- Most forms of pathologic hyperplasia are caused by excessive hormonal or growth factor stimulation. For example, after a normal menstrual period, there is a burst of uterine epithelial proliferation that is normally tightly regulated by stimulation through pituitary hormones and ovarian estrogen and by inhibition through progesterone. However, if the balance between estrogen and progesterone is disturbed, endometrial hyperplasia ensues, a common cause of abnormal menstrual bleeding.

#### Hypertrophy:

- Hypertrophy is an increase in the size of the cells, resulting, increase in the size of the organ
- Increase in DNA content and increasing size of the cell
- There are no newer cell, just bigger cell
- Physiologic: Hypertrophy of skeletal muscle of weight lifters
- Pathological: Cardiac muscle of the hypertensive patient

#### \* Atrophy

- Shrinkage in the size of the cell by the loss of cell substance is known as atrophy.
- The Decrease in cell/organ size and functional ability
- It should be emphasized that although atrophic cells may have diminished function, they are not dead.
- Causes of atrophy include a decreased workload (e.g., immobilization of a limb to permit healing of a fracture), loss of innervation, diminished blood supply, inadequate nutrition, loss of endocrine stimulation, and aging (senile atrophy).

#### Metaplasia:

 Metaplasia is a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type

- Functional change in cell
- Most commonly involve surface epithelium and most common cause is chronic irritation
- The "rugged" stratified squamous epithelium may be able to survive under circumstances that the more fragile specialized epithelium would not tolerate. Although the metaplastic squamous epithelium has survival advantages, important protective mechanisms are lost, such as mucus secretion and ciliary clearance of particulate matter. Epithelial metaplasia is therefore a double-edged sword; moreover, the influences that induce metaplastic transformation, if persistent, may predispose to malignant transformation of the epithelium.
- Metaplasia may also occur in mesenchymal cells but less clearly as an adaptive response.
   For example, bone is occasionally formed in soft tissues, particularly in foci of injury.

#### Example:

- ✓ Vitamin A deficiency
- Habitual cigarette smoking----- The normal ciliated columnar epithelial cells of the trachea and bronchi are focally or widely replaced by <u>stratified squamous epithelial</u> cells.
- ✓ Myositis ossificans: is the formation of bone tissue inside muscle tissue after a traumatic injury to the area, like when a person had swelling in the upper arm due to injury, swelling remained for 3 months by resolved in 1 year is due to metaplasia

#### Dysplasia:

- Reversible Loss of shape, size, and orientation/architecture of the cell
- Increase in N/C ratio
- Dysplasia is encountered principally in the epithelia
- It is a loss in the uniformity of individual cells and in their architectural orientation
- Dysplastic cells exhibit considerable pleomorphism and often possess hyperchromatic nuclei that are abnormally large for the size of the cell
- · Mitotic figures are more abundant than usual

#### ❖ Aplasia:

- · Failure of cell production during embryogenesis
- · e.g. unilateral renal agenesis

#### Hypoplasia

- Decrease in cell production during embryogenesis
- · Result in a relatively small organ
- · e.g. Streak ovary in Turner syndrome

#### Type of Errors in Organ Morphogenesis

- Agenesis ——Absent organ due to absent primordial tissue
- Aplasia———Absent organ despite present primordial tissue
- Deformation—Extrinsic disruption, occurs after the embryonic period
- Malformation—Intrinsic disruption, occur during the embryonic period (weeks 3-8)
- Hypoplasia: ——Incomplete organ development, Primordial tissue present

#### Pathologic Calcification

## Metastatic Calcification Dystrophic Calcification

- Metastatic calcification can occur in normal tissues whenever there is Hypercalcemia
- Dystrophic calcification is encountered in areas of necrosis of any type
- It is virtually inevitable in the atheromas of advanced atherosclerosis
- The four major causes of Hypercalcemia are:
  - √ Hyperparathyroidism
- ✓ Destruction of bone due to the effects of accelerated turnover (e.g. Paget disease), immobilization, or tumors (increased bone catabolism associated with multiple myeloma, leukemia, or diffuse skeletal metastases)
- ✓ Vitamin-D related disorders including vitamin D intoxication and Sarcoidosis (in which macrophages activate a vitamin D precursor)
- Renal failure, in which phosphate retention leads to secondary hyperparathyroidism.
- Commonest site:
  - √ Lungs (commonest site)
  - √ Kidney
  - ✓ Blood vessels (e.g. systemic and pulmonary veins)
  - ✓ Stomach

- Occur in:
  - ✓ Area of old trauma
  - ✓ Atherosclerotic lesions
  - ✓ Tuberculosis lesion
- ✓ Calcification in <u>chronic</u> pancreatitis
- ✓ Dystrophic calcification of the aortic valves is an important cause of aortic stenosis in the elderly
- The pathogenesis of dystrophic calcification involves initiation (or nucleation) and propagation, both of which may be either intracellular or extracellular; the ultimate product is the formation of crystalline calcium phosphate.
- Psammoma bodies are round microscopic calcific collections. It is a form of dystrophic calcification.

  Necrotic cells form the focus for surrounding calcific deposition.

## Acute and chronic inflammation

#### Acute Inflammation

#### Vascular Changes

Vasodilatation and increased vascular permeability are the characteristic features of Acute inflammation

#### · Vasodilatation:

- First or immediate event after the injury is transient vasoconstriction, followed by arteriolar vasodilatation
- Vasodilation is induced by chemical mediators such as histamine

#### · Increase in vascular permeability

Increased vascular permeability is induced by histamine, kinins and other mediators that
produce gaps between endothelial cells, by direct or leukocyte-induced endothelial injury,
and by increased passage of fluids through the endothelium; increased vascular
permeability allows plasma proteins and leukocytes to enter sites of infection or tissue
damage; fluid leak through blood vessels results in edema.

#### Cellular Changes

#### Margination:

CONTRACTOR OF THE REAL PROPERTY.

- . This is the first step
- The process of leukocyte accumulation at the periphery of vessels is called Margination or the displacement of leukocytes by RBC to the periphery of the vessel or increased No. of WBCs in periphery adjacent to endothelium
- Slowing, stagnation of the flow occurs due to increased vascular permeability

#### Rolling: -----slow tumbling and transient adhesion

- Leukocytes tumble on the endothelial surface, transiently sticking along the way, by a process called rolling
- These weak and transient adhesions involved in rolling are mediated by the selectin family
  of adhesion molecules

#### · Pavementation:

Complete Lining up of adhered leukocyte along vessels wall, endothelium appeared to be
essentially lined up by white cells

#### · Adhesion

- . The next step in the reaction of leukocytes is firm adhesion to endothelial surfaces
- Rolling comes to stop and adhesion result
- This adhesion is mediated by Integrins expressed on leukocyte cell surfaces interacting with their ligands on endothelial cells
- Endothelial:----ICAM-1 and VCAM-1
- Leukocytes: ----LFA-1, mac-1, VLA-4
- ICAM-1 bind LFA-1/ mac-1 and VCAM-1 bind VLA-4

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## Migration: (also called Emigration, Extravasations, Diapedesis)

• After being arrested on the endothelial surface, leukocytes migrate through the vessel wall primarily by squeezing between cells at intercellular junctions (although intracellular movement through endothelial cell cytoplasm has also been described). This movement of leukocytes, called diapedesis, occurs mainly in the postcapillary venules of the systemic vasculature; it has also been noted in capillaries in the pulmonary circulation.

#### Chemotaxis:

- After extravasating from the blood, leukocytes migrate toward sites of infection or injury along a chemical gradient by a process called chemotaxis.
- Both exogenous and endogenous substances can be chemotactic for leukocytes
- · Chemotaxis: Chemotaxis implies directed locomotion
- · Chemokinesis: Enhanced random movement
- · Chemotactic factors:
  - V 11-
  - ✓ LTB4: LTB4 is a potent chemotactic agent and activator of neutrophil functional responses (Reference: Robbins Basic Pathology 7th edition P.64)
  - C5a: C5a is a powerful chemotactic agent for neutrophils, monocytes, eosinophils, and basophils. (Reference: Robbins Basic Pathology 7th edition P.70)
  - √ Kallikreins
  - ✓ Bacterial products

#### Leukocyte activation:

- Once leukocytes have been recruited to the site of infection or tissue necrosis, they must be activated to perform their functions. Stimuli for activation include microbes, products of necrotic cells, and several mediators
- Leukocytes express on their surface different kinds of receptors that sense the presence of microbes. These include Toll-like receptors, which recognize endotoxin (LPS) and many other bacterial and viral products

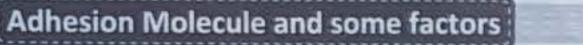
#### Phagocytosis

- Phagocytosis consists of three distinct but interrelated steps: (1) recognition and attachment of the particle to the ingesting leukocyte; (2) engulfment, with subsequent formation of a phagocytic vacuole; and (3) killing and degradation of the ingested material.
- Leukocytes bind and ingest most microorganisms and dead cells via specific surface receptors, which recognize either components of the microbes and dead cells, or host proteins, called opsonins, that coat microbes and target them for phagocytosis (a process called opsonization).
- Chédiak-Higashi syndrome is a rare autosomal recessive disorder that arises from a
  mutation of a lysosomal trafficking regulator protein, which leads to a decrease in
  phagocytosis. The decrease in phagocytosis results in recurrent Pyogenic infections,
  albinism and peripheral neuropathy.
- Important Opsonins are:
  - ✓ C3b and
  - ✓ Fc portion of the IgG

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#### Killing and Degradation of Microbes:

- The culmination of the phagocytosis of microbes is the killing and degradation of the ingested particles. The key steps in this reaction are the production of microbicidal substances within lysosomes and the fusion of the lysosomes with phagosomes, thus selectively exposing the ingested particles to the destructive mechanisms of the leukocytes. The most important microbicidal substances are reactive oxygen species and lysosomal enzymes.
- Phagocytosis stimulates an oxidative burst characterized by a sudden increase in oxygen consumption, glycogen catabolism (glycogenolysis), increased glucose oxidation, and production of ROS.
- The generation of the oxygen metabolites is due to rapid activation of a leukocyte NADPH oxidase, called the phagocyte oxidase, which oxidizes NADPH (reduced nicotinamide adenine dinucleotide phosphate) and, in the process, converts oxygen to superoxide ion
- The dead microorganisms are then degraded by the action of lysosomal acid hydrolases. Perhaps the most important lysosomal enzyme involved in the bacterial killing is elastase.





#### Selectin:

- Induce by IL-1 and TNF (macrophage is the main source of IL-1 and TNF)
- Produce by endothelial cell
- Cause rolling of neutrophil
- The three members of this family are:
  - ✓ E-selectin, expressed on Endothelial cells
  - ✓ P-selectin, present on endothelium and Platelets; and
  - ✓ L-selectin, on the surface of most Leukocytes

#### Integrins:

- Induced by C5a and LTB4
- Present on leukocyte/WBC

#### · Fibronectin:

- · Fibronectin is a large (450-kD) disulfide-linked heterodimer synthesized by a variety of cells, including fibroblasts, monocytes, and endothelium. Fibronectin messenger RNA (mRNA) has two splice forms, which generate tissue and plasma fibronectin.
- Tissue fibronectin forms fibrillar aggregates at wound healing sites; plasma fibronectin binds to fibrin to form the provisional blood clot of a wound, which serves as the substratum for ECM deposition and re-epithelialization.
- Fibronectin is a glycoprotein with the following characteristic
  - ✓ It is a chemotactic for fibroblast and endothelial cell
  - It promotes angiogenesis (new vessel formation)

#### & Laminin:

- Laminin is the most abundant glycoprotein in the basement membrane.
- It is an 820-kD cross-shaped heterotrimer that connects cells to underlying ECM components such as type IV collagen and heparan sulfate.
- Besides mediating attachment to the basement membrane, laminin can also modulate cell proliferation, differentiation, and motility.
- Laminin is glycoprotein while collagen type 4 is not

## Chemical Mediators of inflammation and Their Role



#### . Histamine:

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- Principal mediator of the immediate phase of increased vascular permeability, inducing venular endothelial contraction and interendothelial gaps.
- Finger cut suddenly, inflammation in this condition Is due to histamine because it is the principal mediator of the immediate phase
- It is the most important immediate mediator of inflammation.
- Delayed mediator of inflammation are: Leukotriene and prostaglandins
- Histamine is liberated from: Basophils, Mast cells and Platelets----BMP

#### · Serotonin:

- Serotonin (5-hydroxytryptamine) is also a preformed vasoactive mediator, with effects similar to those of histamine. It is found primarily within platelet dense body granules (along with histamine, adenosine diphosphate, and calcium) and is released during platelet aggregation. Serotonin is secreted from enterochromaffin cells eventually finds its way out of tissue into the blood. There it actively taken up by platelet, which stores it.
- Dopamine promotes seminal emission/ejaculation via D2 receptors, serotonin is inhibitory.

#### · Arachidonic Acid Metabolites:

- Cyclooxygenase stimulates the synthesis of prostaglandins and thromboxanes, and lipoxygenase is responsible for the production of leukotrienes and lipoxins
- The main function of prostaglandin Is Vasodilation

#### Bradykinin:

- Increase vascular permeability---this is the main function of bradykinin in acute inflammation
- Potent vasodilator

#### ❖ TXA2:

- A potent platelet-aggregating agent and vasoconstrictor
- Platelet contain TXA2
- Inhibit by aspirin

#### PGI<sub>2</sub> (Prostacyclin):

- Powerful vasodilator and inhibit platelet aggregation
- Endothelial cell contain PGI<sub>2</sub> (Prostacyclin)

#### Fever and pain:

- Pain: Bradykinin and Prostaglandin-----Bradykinin>>>Prostaglandin
- Fever: IL-1 and TNF-----IL-1 >>>TNF

#### Vasodilator:

Prostaglandin , Histamine and Nitric oxide

#### Interleukin -6:

- IL-6 more than 500 in amniotic fluid is indicative of intra-embryonic infection
- It is the last mediator of endotoxic shock

#### \* Interleukin -8: Functions

- IL-8, also known as neutrophil chemotactic factor, has two primary functions.
  - ✓ It induces chemotaxis in target cells, primarily neutrophils but also other granulocytes, causing them to migrate toward the site of infection.
  - ✓ IL-8 also stimulates phagocytosis once they have arrived.

#### - Oction

#### · Neutrophil:

- It is the primary leukocyte in acute inflammation
- In most forms of acute inflammation, neutrophils predominate in the inflammatory infiltrate during the <u>first 6 to 24 hours</u> and are replaced by monocytes in 24 to 48 hours

Cells of Acute and Chronic Inflammation

- . It is the major circulating phagocytic cell
- \* 02 dependent MPO system is only present in neutrophil and monocytes
- . The Average half-life of neutrophil in circulation is 6 hour
- Contain enzyme Elastase, nicotine is Neutrophilic Elastase inhibitor
- Multilobed nucleus
- Hypersegmented plays (5 or more lobes) are seen in vitamin B12/folate deficiency
- · Pus contains dead neutrophil
- It is responsible for suppuration in abscess
- Activated by IL-8

#### · Basophile:

- Increase in CML and Polycythemia, decrease in Hodgkin lymphoma
- IgE bind on its surface in blood vessel
- Basophilic white blood cells stain dark blue, Esoinophillic white blood cell stain bright red, neutrophils stain a neutral pink.
- Normally, basophils make up less than 1 percent of circulating white blood cells.

#### · Eosinophils:

- Eosinophils are characteristically found in inflammatory sites around parasitic infections or as part of immune reactions mediated by IgE, typically associated with allergies.
- These are the Predominant cell in chronic rhinitis
- Nucleus: central or eccentric, 2-3 lobes; purplish-blue "spectacle shaped"
- Granules: large, coarse; crimson red
- Life span: 8-12 days
- · Function: elevated in Parasitic infestation and allergic reaction

#### ❖ Mast cell:

- Mast cells are sentinel cells widely distributed in connective tissues throughout the body,
   and they can participate in both acute and chronic inflammatory responses.
- IgE-armed mast cells are central players in allergic reactions, including anaphylactic shock
- Mast cells are abundant in the area rich in connective tissue e.g. beneath the epithelium
- Mast cell granules can naturally induce Metachromatic staining
- Heparin naturally produced by mast cells in the body. Basophile also secret heparin.
- Mast cell are abundant in lung and liver
- Mast cell histology show metachromasia

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- Monocytes:
  - Monocytes leave the circulation and become macrophages
  - The half-life of circulating monocytes is about 1 day
  - When monocytes reach the extravascular tissue, they undergo transformation into larger macrophages, which have longer half-lives and a greater capacity for phagocytosis than do blood monocytes.
  - . They do not renter into circulation
  - It is not a phagocytic cell
  - Large kidney or bean-shaped nucleus is characteristic
  - Extensive "frosted glass" Cytoplasm

#### Macrophage:

- Macrophages, the dominant cells of chronic inflammation, are tissue cells derived from circulating blood monocytes after their emigration from the bloodstream-----key cell in chronic inflammation
- Macrophage is the prima donnas (main working cell) of chronic inflammation, while lymphocyte are present in the increased number
- Cause segregation and digestion of foreign bodies

#### Macrophage And Neutrophil Response To Inflammation Lines Of Defense



- The Response of macrophage and neutrophil to inflammation occur at four stages called the line of defense
  - ✓ Ist line of defense-----Tissue macrophage
  - √ 2<sup>nd</sup> line of defense------Neutrophil invasion of inflamed area and Neutrophilia
  - √ 3<sup>rd</sup> line of defense

    ——Monocytes macrophage invasion of the inflamed area
  - ✓ 4th line of defense----increase the production of granulocytes and monocytes by bone marrow

#### **Naseem Sherzad High-Yield Points**

- The Most common site of pressure sore is the ischium.
- The Most common site for keloid is sternum
- Keloid is due to the proliferation of immature fibroblastic tissue and it extends beyond the boundary of the wound
- Fibroblast are maximum in number following an injury after 7 days

Red Infarct	Pale Infarct
Occur in: Tissue with dual or multiple blood supplies like lung, in loose tissues (such as lung), with venous occlusions (such as in ovarian torsion); Reperfusion injury is due to damage by free radical (activated O2 species)	Occur with arterial occlusion in solid organ
Example:  ✓ Liver  ✓ Lung  ✓ Testis, Intestine	Example: KHS  ✓ Kidney  ✓ Heart  ✓ Spleen

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#### **Free Radicals**

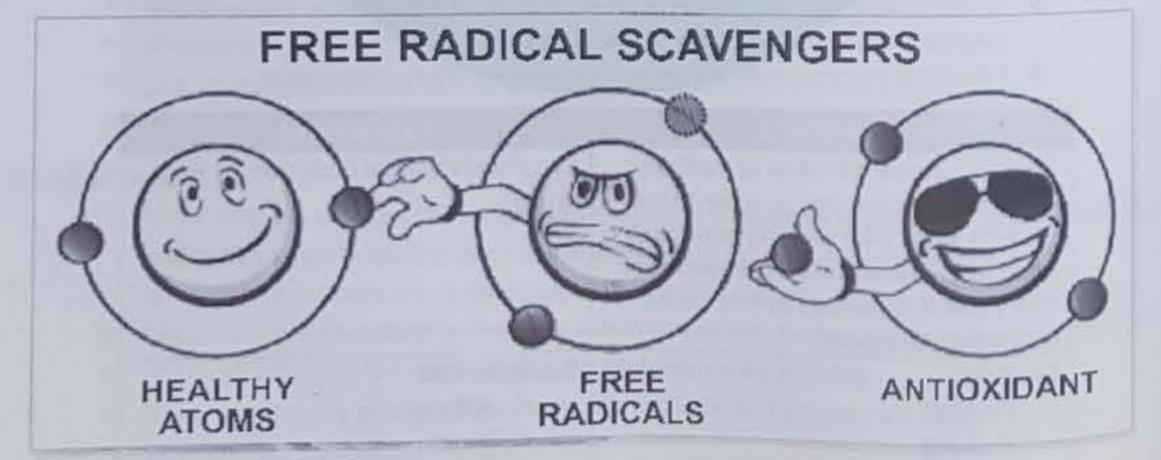
- · Free radicals are chemical species that contain single unpaired electron in an outer orbit
- Free radical damage cell via lipid peroxidation, protein modification and DNA breakage
- Initiated via radiation exposure, metabolism of drugs, redox reaction, nitric oxide, leukocyte oxidative burst
- In radiation Free radical are responsible for causing cancer
- Free radical can be eliminated by:
  - ✓ Enzymes like: Catalase, Superoxide dismutase, glutathione peroxidase
  - ✓ Spontaneous decay
  - ✓ Antioxidants like vitamin A, C, E
  - ✓ Most potent antioxidant-----Glutathione> vitamin E> vitamin C
- Tissue damage by ionizing radiation is due to the formation of hydroxy free radical
- In brain free radical are detoxified by superoxide dismutase
- Superoxide dismutase is responsible for oxygen-dependent killing

#### Fenton reaction

- ✓ A mixture of hydrogen peroxide and an iron (II) salt causes the formation of hydroxyl radical.

#### Generation of free radicals:

- ✓ Redox reaction: e.g. oxidative phosphorylation In mitochondria
- ✓ Enzymatic metabolism of exogenous/endogenous chemical or drugs e.g. CCL4 can generate CCI3
- ✓ Nitric oxide (a potent vasodilator)---Produced by endothelial cell, macrophage, neurons
- ✓ During inflammation—ROS are produced by activated leucocytes



## Edema

Hemodynamic Disorders, Thrombosis and shock

Disease	Cause of Edema
Liver cirrhosis	Hypoalbuminemia
AscitiesMost common cause is:	Liver cirrhosis with Portal Hypertension
Nephrotic syndrome	Hypoalbuminemia
Nephritic syndrome	Due to increase sodium retention
Kwashiorkor	Hypoalbuminemia
Burn	Due to the Increase loss of protein (albumin)
Right-sided heart failure	Peripheral edema
Left-sided heart failure	Pulmonary edema
Anasarca	Severe and generalized edema with widespread subcutaneous tissue swelling
Congestive heart failure	Edema is due to increase in the hydrostatic pressure secondary to the increase in venous pressure

#### Edema due to lymphatic obstruction: (Lymphoedema)

- ✓ Malignant infiltration
- ✓ Radiation injury
- ✓ Congenital abnormality-----Milroy's disease
- ✓ Elephantiasis

### Six factors can contribute to the formation of edema:

- 1. Increased hydrostatic pressure;
- 2. Reduced colloidal or oncotic pressure within blood vessels
- 3. Increased tissue colloidal or oncotic pressure
- 4. Increased blood vessel wall permeability (e.g., inflammation)
- 5. Obstruction of fluid clearance in the lymphatic system
- 6. Changes in the water-retaining properties of the tissues

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#### Difference between Transudates and exudates

Transudates	Exudates	
T- Transparent, Thin	Turbid, bloody	
Due to increased hydrostatic pressure	Due to increase permeability	
Low protein, clear	Rich in protein esp. fibrin (cloud)	
Fluid total Protein: 30g/L—3gm/dl or less	Fluid total Protein >30g/L-3g/dl	
No inflammatory cell	Contain inflammatory cell, RBC	
Low specific gravity <1.012	High specific gravity >1.012	
Does not coagulate	Coagulate—due to fibrinogen etc	
Occur early in inflammation	Occur late in inflammation	
Just fluid	Plasma protein and leukocytes	
Diseases: CHF and liver cirrhosis	Diseases: inflammatory conditions	
White blood cell count: <1000/μl	White blood cell count: >1000/ μl	

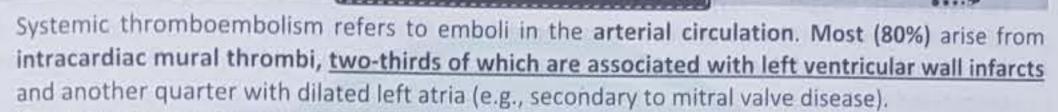
#### Thrombosis

- The pathologic form of hemostasis is thrombosis; it involves blood clot (thrombus) formation in uninjured vessels or thrombotic occlusion of a vessel after relatively minor injury.
- Both hemostasis and thrombosis involve three components: the vascular wall, platelets, and the coagulation cascade.
- There are three primary influences on thrombus formation (called Virchow's triad): (1) endothelial injury, (2) stasis or turbulence of blood flow, and (3) blood hypercoagulability
- Hypercoagulability:
  - ✓ It is loosely defined as any alteration of the coagulation pathways that predispose to thrombosis, and it can be divided into primary (genetic) and secondary (acquired) disorders
    - o Primary (Genetic or inherited): Of the inherited causes of hypercoagulability, mutations in the factor V gene and the prothrombin gene are the most common
    - o Secondary (Acquired): Prolonged bed rest or immobilization, Myocardial infarction, Atrial fibrillation, Tissue damage (surgery, fracture, burns), Cancer, Antiphospholipid antibody syndrome etc., condition with low risk for thrombosis include OCP, pregnancy, nephrotic syndrome, smoking and sickle cell anemia
- Thrombi can have grossly (and microscopically) apparent laminations called lines of Zahn; these represent pale platelet and fibrin layers alternating with darker erythrocyte-rich layers. Such lines are significant only in that they represent thrombosis in the setting of flowing blood; their presence can therefore potentially distinguish antemortem thrombosis from the bland nonlaminated clots that occur in the postmortem state.
- Most venous thrombi occur in the superficial or deep veins of the leg. Superficial venous thrombi usually occur in the saphenous system, particularly when there are varicosities
- Deep thrombi in the larger leg veins at or above the knee joint (e.g., popliteal, femoral, and iliac veins) are more serious because they may embolize. Cardiac failure is an obvious reason for stasis

in the venous circulation. Trauma, surgery, and burns usually result in reduced physical activity, injury to vessels, release of procoagulant substances from tissues, and/or reduced t-PA activity

- Regardless of the specific clinical setting, advanced age, bed rest, and immobilization increase the risk of deep venous thrombosis because reduced physical activity diminishes the milking action of muscles in the lower leg and so slows venous return.
- The Correct sequence of events in valve damage (DTBP): Damaged valve---Thrombus-----Bacteremia-----Perforation
- Elevated plasma homocysteine is associated with an increased risk of atherosclerosis and thrombosis

#### Systemic Thromboembolism



- In contrast to venous emboli, which tend to lodge primarily in one vascular bed (the lung), arterial emboli can travel to a wide variety of sites; the site of arrest depends on the point of origin of the thromboembolus and the relative blood flow through the downstream tissues.
- . The major sites for arteriolar embolization are the lower extremities (75%) and the brain (10%), with the intestines, kidneys, and spleen affected to a lesser extent.
- A very small fraction of systemic emboli appear to arise in veins but end up in the arterial circulation, through interventricular defects. These are called paradoxical emboli.
- The most common cause of mesenteric ischemia is an arterial embolus

#### Fat embolism

- Microscopic fat globules can be found in the circulation after fractures of long bones (which contain fatty marrow) or after soft-tissue trauma.
- Fat embolism syndrome is characterized by pulmonary insufficiency, neurologic symptoms, anemia, and thrombocytopenia
- It is fatal in about 10% of cases.
- Typically, the symptoms appear 1 to 3 days after injury, with sudden onset of tachypnea, dyspnea, and tachycardia. Neurologic symptoms include irritability and restlessness, with progression to delirium or coma.

#### Air embolism

- Gas bubbles within the circulation can obstruct vascular flow (and cause distal ischemic injury) almost as readily as thrombotic masses can.
- Air may enter the circulation during obstetric procedures or as a consequence of chest wall injury.
- Generally, more than 100mL of air is required to produce a clinical effect; bubbles can coalesce to form frothy masses sufficiently large to occlude major vessels.

### Amniotic Fluid Embolism

- Amniotic fluid embolism is a grave but fortunately uncommon complication of labor and the immediate postpartum period (1 in 50,000 deliveries).
- It has a mortality rate in excess of 20% to 40%.
- The onset is characterized by sudden severe dyspnea, cyanosis, and hypotensive shock, followed by seizures and coma.

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### N....

### **Decompression Sickness**



- Form of gas embolism
- Common in deep-sea diving
- Nitrogen gas is forced out of alveoli and dissolved in blood and tissue
- Caisson disease: caused by persistence of gas emboli in bone, producing aseptic necrosis (bone infarction)
- Tx: Hyperbaric oxygen—Hyperbaric O₂ is also used for Tx of gas gangrenes and CO poisoning, if all three are given in the stem, decompression sickness should be on top—
- The Complication of hyperbaric O<sub>2</sub>: Pneumothorax, myopia, middle ear Barotrauma and oxygen-induced seizure

### Fever, Temperature and Means of Heat Loss



- The Rectal temperature at which permanent cell death occur----106°C
- The Temperature at which skin burn occur-----45°C
- Intra-testicular temperature is less than abdominal temperature——2-3°C
- Intra-testicular temperature less than rectal temperature——1-2°C
- Rectal temperature is about 0.5% higher than oral
- Body temperature is highest in the evening and lowest in early morning
- Body temperature is subnormal in old age due to decrease BMR
- Body temperature falls during menstruation and maximum after ovulation
- In general anesthesia body temperature decrease due to depressed activity of ascending reticular system
- The first physiological response to high environmental temperature is vasodilation
- The most Accurate noninvasive index of core temperature is the esophageal temperature (esophageal> rectal> oral)
- When the hypothalamus set point temperature is increased above the core body temperature, the body will respond by increasing shivering (potent mechanism for heat gain) and by decreasing sweating.
- Mechanism of fever:
  - ✓ Pyogenes increase the production of IL-1 in phagocytic cell
  - ✓ IL-1 acts on the anterior hypothalamus to increase the production of prostaglandin
  - ✓ Formation of Prostaglandin E1 in cell of hypothalamus increase the set-point temperature and produce fever

#### **Means of Heat Loss**

- Patient with ETT/ tube or Tracheostomy, heat lost by----Evaporation
- Patient naked heat lost by----radiation (in form of infra-red rays)
- Patient naked and temperature mentioned in stem-----Radiation
- Patient naked and lying (contact with table etc.)-----Conduction
- ❖ When humidity mentioned———————Convection

## Tissue and Wound Repair

Repair refers to the restoration of tissue architecture and function after an injury. It occurs by two types of reactions.

Some tissues are able to replace the damaged components and essentially return to a normal state; this process is called regeneration.

- If the injured tissues are incapable of complete restitution, or if the supporting structures of the tissue are severely damaged, repair occurs by laying down of connective (fibrous) tissue, a process termed healing that results in scar formation.
- Although the fibrous scar is not normal, it provides enough structural stability that the injured tissue is usually able to function.
- After many common types of injury, both regeneration and scar formation contribute in varying degrees to the ultimate repair. The term fibrosis is most often used to describe the extensive deposition of collagen that occurs in the lungs, liver, kidney, and other organs as a consequence of chronic inflammation, or in the myocardium after extensive ischemic necrosis (infarction). If fibrosis develops in a tissue space occupied by an inflammatory exudate it is called organization (as in organizing pneumonia affecting the lung).
- ❖ A mature sac is differentiated from granulation tissue in that it has more cross-linked collagen
- In injured tissues, fibroblasts are activated and differentiate into myofibroblasts, which contract and participate in open wound healing by reducing the size of wound and secreting ECM proteins. The differentiation of fibroblasts to myofibroblasts is a key event in connective tissue wound healing

Mediators		Role	
Fibroblast Growth Factors	FGF	Stimulate angiogenesis	
Transforming Growth Factor Beta	TGF-β	<ul> <li>Angiogenesis, fibrosis</li> <li>TGF-β induces apoptosis, or programmed cell death, in human lymphocytes and hepatocytes.</li> <li>It causes immunosuppression and angiogenesis, which makes the cancer more invasive</li> </ul>	
Vascular Endothelial Growth Factor	VEGF	<ul> <li>Stimulate angiogenesis</li> <li>Most important growth factor in adult tissue undergoing physiologic angiogenesis as well as angiogenesis occurring in chronic inflammation, wound healing, tumor and diabetic retinopathy</li> </ul>	
Platelet-Derived Growth factor	PDGF	<ul> <li>Secreted by activated platelets and macrophages</li> <li>Key regulator of cell metabolism and growth</li> <li>Induce vascular remodeling and smooth Muscle cell migration</li> <li>Stimulate fibroblast growth for collagens synthesis</li> </ul>	
Metalloproteinases		Tissue remodelingvery important	
Epidermal Growth Factor	EGF	<ul> <li>Stimulate cell growth via tyrosine kinase</li> <li>Liver regeneration occur through EGF</li> </ul>	

**General Pathology** 

#### Factor affecting Wound Healing

#### . Local:

- ✓ Infection----most common
- √ Oxygenation
- √ Foreign body
- √ Venous insufficiency

#### Systemic

- ✓ Hormone: such as glucocorticoid, have an anti-inflammatory effect and inhibit collagen synthesis
- ✓ Vitamin c deficiency—lead to a defect in wound healing, particularly via a failure in collagen synthesis and cross-linking
- ✓ Zinc deficiency: decreased fibroblast proliferation, decreased collagen synthesis, impaired overall wound strength and delayed epithelialization
- ✓ Stress and Ischemia
- ✓ Diabetes and Obesity
- ✓ Alcoholism and smoking
- ✓ Anemia and malnutrition

#### Primary Healing and Secondary Healing

#### Primary union (healing by first intention):

- One of the simplest examples of wound repair is the healing of a clean, uninfected surgical incision approximated by surgical sutures. This is referred to as primary union, or healing by first intention.
- The incision causes only focal disruption of epithelial basement membrane continuity and death of a relatively few epithelial and connective tissue cells. As a result, epithelial regeneration predominates over fibrosis.
- A small scar is formed, but there is minimal wound contraction. The narrow incisional space
  first fills with fibrin-clotted blood, which is rapidly invaded by granulation tissue and covered
  by new epithelium.
- Within 24 hours, neutrophils are seen at the incision margin, migrating toward the fibrin clot. Basal cells at the cut edge of the epidermis begin to show increased mitotic activity. Within 24 to 48 hours, epithelial cells from both edges have begun to migrate and proliferate along the dermis, depositing basement membrane components as they progress. The cells meet in the midline beneath the surface scab, yielding a thin but continuous epithelial layer.
- By day 3, neutrophils have been largely replaced by macrophages, and granulation tissue progressively invades the incision space. Collagen fibers are now evident at the incision margins, but these are vertically oriented and do not bridge the incision. Epithelial cell proliferation continues, yielding a thickened epidermal covering layer.
- By day 5, neovascularization reaches its peak as granulation tissue fills the incisional space.
   Collagen fibrils become more abundant and begin to bridge the incision. The epidermis recovers its normal thickness as differentiation of surface cells yields a mature epidermal architecture with surface keratinization.

- During the second week, there is continued collagen accumulation and fibroblast proliferation. The leukocyte in iltrate, edema, and increased vascularity are substantially diminished. The long process of "blanching" begins, accomplished by increasing collagen deposition within the incisional scar and the regression of vascular channels.
- By the end of the first month, the scar comprises a cellular connective tissue largely devoid of inflammatory cells and covered by an essentially normal epidermis. However, the dermal appendages destroyed in the line of the incision are permanently lost.
- The strength of surgical wound depended on the type of collagen produced

### Secondary union (healing by secondary intention)

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- When cell or tissue loss is more extensive, such as in large wounds, abscess formation, and ulceration, the repair process is more complex, as is also the case after infarction in parenchymal organs. In second-intention healing, also known as healing by secondary union, the inflammatory reaction is more intense, there is abundant development of granulation tissue, and the wound contracts by the action of myofibroblasts. This is followed by accumulation of ECM and formation of a large scar.
- A larger clot or scab rich in fibrin and fibronectin forms at the surface of the wound.
   Inflammation is more intense because large tissue defects have a greater volume of necrotic debris, exudate, and fibrin that must be removed. Consequently, large defects have a greater potential for secondary, inflammation-mediated, injury.
- Much larger amounts of granulation tissue are formed.
- Larger defects require a greater volume of granulation tissue to fill in the gaps and provide the underlying framework for the regrowth of tissue epithelium.
- A greater volume of granulation tissue generally results in a greater mass of scar tissue.

#### Secondary healing involves wound contraction.

- ✓ Within 6 weeks, for example, large skin defects may be reduced to 5% to 10% of their original size, largely by contraction.
- ✓ This process has been ascribed to the presence of myofibroblasts, which are modified fibroblasts exhibiting many of the ultrastructural and functional features of contractile smooth muscle cells. Wound contraction commences on about 4<sup>th</sup> day after injury
- ✓ Wound contraction should not be confused with wound contracture where scar formation over a joint interferes with mobility

#### **Wound Strength**

- Carefully sutured wounds have approximately 70% of the strength of unwounded skin, largely because of the placement of the sutures.
- When sutures are removed, usually at 1 week, wound strength is approximately 10% of that of unwounded skin, but this increases rapidly over the next 4 weeks.
- The recovery of tensile strength results from collagen synthesis exceeding degradation during the first 2 months, and from structural modifications of collagen (e.g., cross-linking and increased fiber size) when synthesis declines at later times.
- Wound strength reaches approximately 70% to 80% of normal by 3 months or 12<sup>th</sup> week but usually does not substantially improve beyond that point.

### **Amyloidosis**

- Amyloidosis is a condition associated with a number of inherited and inflammatory disorders in which extracellular deposits of fibrillar proteins are responsible for tissue damage and functional compromise. Amyloidosis is fundamentally a disorder of protein misfolding.
- Amyloid is not a structurally homogeneous protein, although it always has the same morphologic appearance. In fact, more than 20 (at last count, 23) different proteins can aggregate and form fibrils with the appearance of amyloid. Regardless of their derivation, all amyloid deposits are composed of nonbranching fibrils, 7.5 to 10 nm in diameter, each formed of \beta-sheet polypeptide chains that are wound together.
- The dye Congo red binds to these fibrils and produces a red-green dichroism (birefringence), which is commonly used to identify amyloid deposits in tissues.
- Under polarized light, Congo stained amyloid exhibit apple-green birefringence
- Of the more than 20 biochemically distinct forms of amyloid proteins that have been identified, three are most common:
  - The AL (amyloid light chain) protein is produced by plasma cells and is made up of complete immunoglobulin (Ig) light chains, the amino-terminal fragments of light chains, or both.
  - ✓ The AA (amyloid-associated) fibril is a unique non-immunoglobulin protein derived from a larger (12-kD) serum precursor called SAA (serum amyloid-associated) protein that is synthesized in the liver. The production of this protein is increased in inflammatory states as part of the "acute phase response"; therefore this form of amyloidosis is associated with chronic inflammatory disorders.
  - Aß amyloid is found in the cerebral lesions of Alzheimer's disease. Aß is a 4-kD peptide that constitutes the core of cerebral plaques and the amyloid deposits in cerebral blood vessels in this disease. The AB protein is derived from a much larger transmembrane glycoprotein called amyloid precursor protein (APP)

#### Classification:

- ✓ Amyloid may be systemic (generalized), involving several organ systems, or it may be localized, when deposits are limited to a single organ, such as the heart.
- On clinical grounds, the systemic, or generalized, pattern is subclassified into primary amyloidosis when associated with some immunocyte dyscrasia, or secondary amyloidosis when it occurs as a complication of an underlying chronic inflammatory or tissue destructive process.
- ✓ Hereditary or familial amyloidosis constitutes a separate, albeit heterogeneous group, with several distinctive patterns of organ involvement.

#### Primary amyloidosis:

- ✓ Amyloid in this category is usually systemic in distribution and is of the AL (amyloid light) chain) type. This is the most common form of amyloidosis.
- ✓ The best example in this category is amyloidosis associated with multiple myeloma, a malignant neoplasm of plasma cells

#### Reactive systemic amyloidosis:

✓ The amyloid deposits in this pattern are systemic in distribution and are composed of AA protein. This category was previously referred to as secondary amyloidosis, because it is secondary to an associated inflammatory condition.

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✓ The feature common to most cases of reactive systemic amyloidosis is protracted cell injury occurring in a spectrum of infectious and noninfectious chronic inflammatory conditions. Classically, tuberculosis, bronchiectasis, and chronic Osteomyelitis were the most common causes; with the advent of effective antimicrobial therapies, reactive systemic amyloidosis is seen most frequently in the setting of chronic inflammation caused by autoimmune states (e.g., RA, Ankylosing spondylitis, and inflammatory bowel disease).

#### Clinical Correlation

- Kidney: Amyloidosis of the kidney is the most common and most serious involvement in the disease. Microscopically, the amyloid deposits are found principally in the glomeruli, but they are also present in the interstitial peritubular tissue as well as in the walls of the blood vessels. The glomerulus first develops focal deposits within the mesangial matrix and diffuse or nodular thickenings of the basement membranes of the capillary loops. With progression, the deposition encroaches on the capillary lumina and eventually leads to the total obliteration of the vascular tuft
- Spleen: Amyloidosis of the spleen often causes moderate or even marked enlargement (200-800)
- · Liver: Amyloidosis of the liver may cause massive enlargement (as much as 9000 gm). In such advanced cases the liver is extremely pale, grayish, and waxy on both the external surface and the cut section. Histologically, amyloid deposits first appear in the space of Disse and then progressively enlarge to encroach on the adjacent hepatic parenchyma and sinusoids
- Heart: Amyloidosis of the heart may occur either as isolated organ involvement or as part of a systemic distribution. When accompanied by systemic involvement, it is usually associated with immunocyte dyscrasias. The isolated form (senile amyloidosis) is usually confined to older individuals.
- Biopsy and subsequent Congo red staining is the most important tool in the diagnosis of amyloidosis. In general, the biopsy is taken from the organ suspected to be involved. For example, renal biopsy is useful in the presence of urinary abnormalities. Rectal and gingival biopsy specimens contain amyloid in as many as 75% of cases with generalized amyloidosis. Examination of abdominal fat aspirates stained with Congo red is a simple, low-risk method. In suspected cases of AL amyloidosis, serum and urinary protein electrophoresis and immunoelectrophoresis should be performed. Bone marrow aspirate in such cases usually shows plasmacytosis, even if skeletal lesions of multiple myeloma are not present.
- Transthyretin (TTR) is a normal serum protein that binds and transports thyroxine and retinol, hence the name. Mutations in the gene encoding transthyretin result in the production of a protein (and its fragments) that aggregate and form amyloid deposits. The resultant diseases are called familial amyloid polyneuropathies. Transthyretin is also deposited in the heart of aged individuals (senile systemic amyloidosis); in such cases the protein is structurally normal, but it accumulates at high concentrations.
- B2-microglobulin, a component of the MHC class I molecules and a normal serum protein, has been identified as the amyloid fibril subunit (AB2m) in amyloidosis that complicates the course of patients on long-term hemodialysis. Aβ2m fibers are structurally similar to normal β2m protein. This protein is present in high concentrations in the serum of patients with renal disease and is retained in the circulation because it is not efficiently filtered through dialysis membranes. In some series, as many as 60% to 80% of patients on long-term dialysis developed amyloid deposits in the synovium, joints, and tendon sheaths.

### **NEOPLASIA**

- Malignant neoplasms that are composed of undifferentiated cells are said to be anaplastic, Lack of differentiation, or anaplasia, is considered a hallmark of malignancy.
- Anaplastic cells display marked pleomorphism (i.e., marked variation in size and shape) Characteristically the nuclei are extremely hyperchromatic (darkly stained) and large.
- The nuclear-to-cytoplasmic ratio may approach 1: 1 instead of the normal 1: 4 or 1: 6.
- The properties of invasiveness and, even more so, metastasis, more unequivocally identify a neoplasm as malignant as any of the other attributes of a tumor.
- Even though most malignant tumors are monoclonal in origin, by the time they become clinically evident, their constituent cells are extremely heterogeneous
- The Lymph node is the most common site for metastasis, site of choice for carcinoma
- NK cells are lymphocytes that are capable of destroying tumor cells without prior sensitization: they may provide the first line of defense against tumor cells.
- Circulating tumor cell most widely diagnosed by peripheral blood film
- Cachexia is a complication of disseminated cancer
- Anemia of chronic disease is the most common anemia in malignancy
- The parenchymal cells in a neoplasm, whether benign or malignant, resemble each other, as though all had been derived from a single progenitor.
- Differentiation and anaplasia refer only to the parenchymal cells that constitute the transformed elements of neoplasms
- . The differentiation of parenchymal cells refers to the extent to which they resemble their normal forebears morphologically and functionally.
- The stroma carrying the blood supply is crucial to the growth of tumors but does not aid in the separation of benign from malignant ones. The amount of stromal connective tissue does determine, however, the consistency of a neoplasm. Certain cancers induce a dense, abundant fibrous stroma (desmoplasia), making them hard, so-called scirrhous tumors.
- Locally malignant tumor include: Ameloblastoma, BCC
- Four Carcinomas Routs Hematogenously: Follicular carcinoma, Choriocarcinoma, RCC, HCC

#### **Naseem Sherzad High-Yield Points**

- Microscopic feature/diagnostic criteria of premalignant Condition-High N/C ratio
- Microscopic feature/diagnostic criteria of premalignant Lesion------Pleomorphism
- Diagnostic criteria for malignant tumor--invasion to adjacent tissue > pleomorphism
- The Best method to detect malignancy is-----Histopathological
- Diagnostic criteria for soft tissue tumor--- Increased vascularity
- Tumor spread by breakdown of-----E-Cadherin
- Most cancer have------Keratin filament
- Difference between benign tumor and hypertrophy----Capsule (derived from stroma)
- Difference between malignant and benign tumor------Mets

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	General Pathology		
Tumor	Explanation		
Chondroma	<ul> <li>A benign tumor arising in fibrous tissue is a Fibroma; a benign cartilaginous tumor is a Chondroma.</li> </ul>		
Liposarcoma	<ul> <li>Liposarcoma is a cancer that arises in fat cells in deep soft tissue, such as that inside the thigh or in the retroperitoneum</li> </ul>		
Chondrosarcoma	A malignant neoplasm composed of chondrocytes is a Chondrosarcoma		
Fibrosarcoma	A cancer of fibrous tissue origin is a Fibrosarcoma		
Carcinomas	Malignant neoplasms of epithelial cell origin are called carcinomas		
Adenocarcinomas	Carcinomas that grow in a glandular pattern are called adenocarcinomas		
Sarcomas	<ul> <li>Malignant neoplasms arising in mesenchymal tissue or its derivatives are called sarcomas</li> <li>Lymphatic spread is more typical of carcinomas, whereas hematogenous spread is favored by sarcomas</li> <li>Sarcoma have increase vascularity</li> </ul>		
Cystic hygroma	Tumor involving lymph vessels is called cystic hygroma		
	It is a malformation that presents as a mass of disorganized tissue indigenous to the particular site.		
Hamartoma	<ul> <li>A Hamartoma is mostly benign. Pulmonary Hamartoma is the most common benign tumor of the lung. X-Ray shows coin lesion</li> <li>Another misnomer is the term choristoma.</li> </ul>		
Choristoma	<ul> <li>This congenital anomaly is better described as a heterotopic rest of cells. For example, a small nodule of well-developed and normally organized pancreatic tissue may be found in the submucosa of the stomach, duodenum, or small intestine.</li> <li>This heterotopic rest may be replete with islets of Langerhans and exocrine glands.</li> <li>The term choristoma, connoting a neoplasm, imparts to the heterotopic rest a gravity far beyond its usual trivial significance.</li> </ul>		
	<ul> <li>It is a growth or tumor of nerve tissue.</li> <li>The term is also used to refer to any swelling of a nerve, even in the absence of abnormal cell growth. In particular, traumatic neuroma results from trauma to a nerve, often during a surgical</li> </ul>		
Neuroma	<ul> <li>procedure.</li> <li>Morton's neuroma affects the foot.</li> <li>Neuromas can be painful, or sometimes, as in the case of acoustic neuromas, can give rise to other symptoms.</li> <li>Neuromas are one of the most common complications following a limb amountation.</li> </ul>		
Verrucous	<ul> <li>It is an uncommon variant of squamous cell carcinoma.</li> <li>This form of cancer is often seen in those who chew tobacco or use snuff orally, so much so that it is sometimes referred to as "Snuff</li> </ul>		

"Verrucous carcinoma invade with "pushing", broad rete-ridge like

squamous tongue that exhibit minimal cellular atypia

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dipper's cancer.

General Pathology

#### Tumor Markers

Tumor markers are used to detect recurrence and response to therapy and should not be used as a primary tool for diagnosis, for diagnosis, we use biopsy

S/No	Tumor marker	Tumor
1.	CA-19-9	Pancreatic Adenocarcinoma
2.	CA-125	Ovarian cancer
3.	Calcitonin	Medullary thyroid carcinoma
4.	Serum thyroglobulin level	Papillary carcinoma
5.	Alpha-fetoprotein	Hepatocellular carcinoma
6.	B-Hcg	Hydatidiform mole and Choriocarcinoma
7.	CEA	70% of colorectal & pancreatic cancers
8.	PSA	Use to follow prostate carcinoma
9.	S100B	Malignant melanoma

#### Handy points:

- Alpha-fetoprotein is normally produced by fetus & in neural tube defect.
- B-hCG is commonly associated with pregnancy
- The Increase in acetylcholinesterase in amniotic fluid is a helpful confirmatory test for neural tube defects.
- PSA test measure total PSA means both free PSA and bound PSA
- Alkaline Phosphatase found in bone, liver, intestine and placenta, and increase mainly in bone and livers disease
- Acid Phosphatase mostly used to detect Carcinoma Prostate.

#### Staging and Grading For All above Tumors

S/No	Carcinoma	Staging/ grading system	
1.	Carcinoma Prostate	Gleason's Score/bases on architecture	
2.	Carcinoma colon	Duke's Staging	
3.	Carcinoma Stomach	Lauren's Classification	
4.	Breast carcinoma	Bloom Richardson grading	
5.	Hodgkin's Lymphoma	Ann Arbor	
6.	Renal cell carcinoma	Fuhrmann's Grading	
7.	Astrocytoma & Meningioma	WHO grading	
8.	Border classification	Border classification of tumors depend or grading (defined as macroscopic and microscopic degree of differentiation of tumor on histopathology	

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## Metastasis is more common than a primary cancer in the following sites

- Lymph node --- (e.g. metastatic breast and lung cancer most common)
- Lungs -----(e.g. metastatic breast cancer most common)
- Liver -----(e.g. metastatic lung cancer is most common)
- Bone----(e.g. metastatic breast cancer is most common)
- Brain-----(e.g. metastatic lung cancer is most common)

## Top three sites for Gynecological malignancy in decreasing order are

- Endometrium
- Ovary
- Cervix

#### Disease Condition Associated with Neoplasm

s/NO	Condition	Neoplasm
1.	Barrett's esophagus	Esophageal carcinoma
2.	Ulcerative colitis	Colonic Adenocarcinoma
3.	Plummer Vinson syndrome	Squamous cell carcinoma of esophagus
4.	Chronic atrophic gastritis, pernicious anemia	Gastric Adenocarcinoma
5.	Cirrhosis (alcoholic, hepatitis B & C)	Hepatocellular carcinoma
6.	Autoimmune disease (Hashimoto's thyroiditis, myasthenia gravis)	Lymphoma
7.	Actinic keratitis	Squamous cell carcinoma of skin
8.	Down syndrome	ALL
9.	Dysplastic nevus	Malignant melanoma
10.	Clonarchis sinensis (liver fluke)	Cholangiocarcinoma
11.	Schistosoma hematobium	squamous cell carcinoma of bladde
12.	Aflatoxin	Hepatocellular carcinoma
13.	H.pylori	Gastric Adenocarcinoma & lymphom

### Benzyne cause------Acute leukemia High fiber diet cause------Low cholesterol level Low fiber diet cause------Colon Adenocarcinoma

- High-fat diet cause------Breast cancer
- Most common carcinogen-----Nitrosamine
- Diethylstilbestrol DES cause-----clear cell carcinoma Adenocarcinoma of the vagina
- Tobacco is the most common external cause for carcinoma

Radon-----cause squamous cell carcinoma

Carcinogens

## CHAPTER

## GENETIC DISORDERS





#### Introduction

- In humans, the normal chromosome count is 46 (i.e., 2n = 46).
- Any exact multiple of the haploid number (n) is called euploid.
- Chromosome numbers such as 3n and 4n are called polyploid.
- Polyploidy generally results in a spontaneous abortion.
- Any number that is not an exact multiple of n is called aneuploidy.
- The chief cause of aneuploidy is the non-disjunction of a homologous pair of chromosomes at the
  first meiotic division or a failure of sister chromatids to separate during the second meiotic
  division.
- Mosaicism is a term used to describe the presence of two or more populations of cells in the same individual.
- Mutation: Mutation means a permanent change in DNA
- The most common form of DNA is BDNA, which is a right-handed, helical DNA, with 10 base pairs per turn. This is the form of DNA found in humans and most organisms.



#### Gene and Genome



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#### · Gene:

- A gene is the basic physical and functional unit of heredity.
- Genes, which are made up of DNA, act as instructions to make molecules called proteins.
- In humans, genes vary in size from a few hundred DNA bases to more than 2 million bases.
- There are 30,000 essential genes which cause the formation of 30,000 types of protein
- Function: genes (DNA molecules) control the formation of mRNA which control the formation of proteins

#### Genome:

 A genome is all the genetic material (DNA) in the chromosome of a particular organism, its size generally given as its total number of base pairs

### Introns vs. Exons

- Introns: Introns are intervening non-coding segment of DNA—(97% of the human genome)
- Exons: Exons contain the actual genetic information coding for the protein (3% of the human genome)

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Genetic Disorder

#### ¥ ....

#### **Genetic Term**

- Genotype:
   It is the genetic makeup of an organism or individual.
  - · Examples:
    - ✓ The gene responsible for eye color.
    - √ The gene responsible for hair color.

#### phenotype:

- Detectable expression of the genotype
- An expressed and observable trait
- · Can't be inherited
- Examples:
- ✓ Phenotype is the physical appearance of that, like hair color, eye color weight etc.
- Phenotypic sex: Phenotypic sex refers to an individual's sex as determined by their internal and external genitalia, expression of secondary sex characteristics, and behavior.
- Codominance: Both alleles contribute to the phenotype of the heterozygote. Example blood group A, B, AB
- Incomplete Penetrance: Not all individuals with a mutual genotype show the mutant phenotypic effects. Example: BRCA1 gene mutation don't always result in the breast or ovarian cancer
- Complete Penetrance: The allele is said to have complete Penetrance if all individuals who have the disease causing-mutation have clinical symptoms of disease
- Variable expressivity: Phenotype varies among individuals with the same genotype. Example: two patient with neurofibromatosis type I may have varying disease severity
- Pleiotropy: One gene contributes to multiple phenotypic effects. Example: PKU causes many seemingly unrelated symptoms, ranging from mental retardation to hair/skin changes
- Twin study: An experiment that asses the genetic and environmental influence on a trait using MZ and MD twin pairs

#### X and Y Chromosom

#### \* X-Chromosome:

 The X-chromosome is a large submetacentric chromosome with many genes on it, most of which are unrelated to sex

#### Y-Chromosome:

- The Y is acrocentric and much smaller
- Only 83 active genes on Y-chromosome, most of which are related to sex

### Nucleotide versus Nucleoside

Nucleotide	Nucleoside
Nucleotide is composed of a nitrogenous base, pentose sugar and a phosphate group	Nucleoside is composed of only a nitrogenous base and a phosphate group
Nucleotide is formed through phosphorylation of nucleoside	It is a component of the nucleotide
A nucleotide is acidic in nature	It is slightly basic in nature

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#### Difference between DNA and RNA

DNA	RNA
<ul> <li>Double strand molecule both run in opposite directions</li> </ul>	Single strand molecule
<ul> <li>Uracil is absent</li> </ul>	<ul> <li>Thymine is absent</li> </ul>
<ul> <li>Sugar moiety is Deoxyribose</li> </ul>	<ul> <li>Sugar moiety is ribose</li> </ul>
<ul> <li>It is the genetic and hereditary material of cells</li> </ul>	<ul> <li>It is involved in the synthesis of protein</li> </ul>
<ul> <li>Hydrolysis of DNA gives————————————————————————————————————</li></ul>	<ul> <li>Types of RNA:</li> <li>✓ mRNAis the longest type</li> <li>✓ tRNAis the smallest type</li> <li>✓ rRNAis the most abundant type</li> </ul>

#### Barr Body

- Barr body is inactivated X-chromosome, Transcriptionally inactive, seen under light microscope
- Barr body is visible in interphase during this stage DNA replication also occur
- Site for barr body ---- Buccal mucosa
- Barr body attach with cell membrane
- Karyotyping is done in metaphase
- OX----zero barr body----like a normal male
- XX-----one barr body-----like a normal female
- XXX-----2 barr body
- 47XXy -----Klinefelter syndrome—single bar body---which is diagnostic for Klinefelter syndrome
- 45X0---zero barr body---scanty barr body is diagnostic for turner syndrome

#### **Autosomal Recessive**

- All siblings have a chance of one into four of contracting this disease---1:4
- . Autosomal recessive diseases make up the largest group of Mendelian disorders.
- \* They occur when both of the alleles at a given gene locus are mutants; therefore, such disorders are characterized by the following features:
  - The trait does not usually affect the parents, but siblings may show the disease
  - Siblings have one chance in four of being affected (i.e., the recurrence risk is 25% for each birth)
  - If the mutant gene occurs with a low frequency in the population, there is a strong likelihood that the Proband is the product of a consanguineous marriage.

#### Examples:

- Hemochromatosis-----Most common
- Alpha-1 antitrypsin deficiency
- Autosomal Recessive polycystic kidney disease: (ARPKD)--infantile PKD
- Cystic fibrosis
- Wilson disease

#### Congenital adrenal hyperplasia

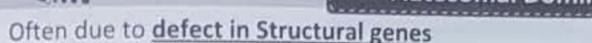
- Thalassemia and sickle cell disease
- Glycogen Storage disease

#### . Two Important Differences:

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- Proband: Proband is the first affected family member who seek medical attention
- Prozone phenomena: An agglutination precipitation reaction, the zone of relatively high antibody concentration within which no reaction occurs. As the antibody concentration is lowered below the Prozone, the reaction occurs. (Solve by dilution). This phenomena may be due simply to antibody excess or it may be due to blocking antibody or to nonspecific inhibitors in serum.

#### Autosomal Dominant



- Often pleiotropic, family history crucial to diagnosis
- The child can be affected if only one of the parent affected
- Autosomal dominant disorders are manifested in the heterozygous state, so at least one parent of an index case is usually affected; both males and females are affected, and both can transmit the condition. When an affected person marries an unaffected one, every child has one chance in two of having the disease.

#### √ Von Willebrand disorder---most common

- ✓ Achondroplasia—the failure of longitudinal bone growth (endochondral ossification)——— short limbs (caused by a gain in function mutation in the FGFR3 gene located on the short arm of Chromosome 4, which affects enchondral bone formation )
- Retinoblastoma
- ✓ Hereditary spherocytosis
- Autosomal Dominant Adult polycystic disease(ADPKD)
- Osteogenesis imperfecta
- Neurofibromatosis
- Pseudohypoparathyroidism
- Familial polyposis coli
- Myotonic dystrophy
- ✓ Marfan syndrome and Acute intermittent porphyria

### X-Linked Disorder

#### 1) X-linked recessive

- Male are commonly more affected than female
- Most X-linked disorders are X-linked recessive
- All sex-linked disorders are X-linked. No Y-linked diseases are as yet known. Save for determinants that dictate male differentiation, the only characteristic that may be located on the Y chromosome is the attribute of hairy ears, which is not altogether devastating.
- They are transmitted by heterozygous female carriers only to sons, who of course are hemizygous for the X chromosome.
- Heterozygous females rarely express the full phenotypic change, because they have the paired normal allele; however, because of the inactivation of one of the X chromosomes in females, it is remotely possible for the normal allele to be inactivated in most cells, permitting full expression of the disease in heterozygous females. An affected male does

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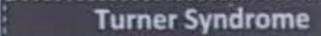
Genetic Disorder

not transmit the disorder to sons, but all daughters are carriers. Sons of heterozygous women have one chance in two of receiving the mutant gene.

Example: Hemophilia A and B, Duchene muscular dystrophy

#### 2) X-linked dominant

- X-linked dominant inheritance, sometimes-referred to as X-linked dominance, is a mode of genetic inheritance by which a dominant gene is carried on the X chromosome. As an inheritance pattern, it is less common than the X-linked recessive type.
- Example: Rett syndrome, the X-linked lissencephaly and double-cortex syndrome, and incontinentia pigmenti type 1, characterized by dermatological, ocular, dental, and neurological abnormalities.



- Also known as "Monosomy X"
- The most common cause of primary amenorrhea in women
- \* Turner syndrome, characterized by primary hypogonadism in phenotypic females, results from partial or complete monosomy of the short arm of the X chromosome
- The Diagnosis is established by karyotyping for chromosomal analysis which will show Karyotype 45 X0
- Clinical features: SWT
  - In adult patients, a combination of Short stature and primary amenorrhea should prompt strong suspicion of Turner syndrome
  - Webbed neck-caused by dilated lymphatic channels-cystic hygroma
  - Associated with preductal Coarctation, bicuspid aortic valve, Horseshoes kidney

#### **Down Syndrome**

- Down syndrome is the most common of the chromosomal disorders
- About 95% of affected persons have trisomy 21, so their chromosome count is 47.
- The parents of such children have a normal karyotype and are normal in all respects
- . Maternal age has a strong influence on the incidence of Down syndrome
- Indeed, in 95% of cases, the extra chromosome is of maternal origin.
- Association:
  - Risk of Down syndrome in the next child –33%
  - Robertsonian translocation--- 4 %
  - Non-disjunction----90%
  - Associated with ASD, AML, hypothyroidism
  - Increase risk of Alzheimer disease

#### Clinical features:

- Characteristic clinical features of Down syndrome include epicanthic folds and flat facial profile
- Protruding tongue and umbilical hernia are typical clinical features
- Trisomy 21 is a leading cause of mental retardation. The degree of mental retardation is severe: IQ varies from 25 to 50
- Congenital malformations are common and quite disabling.
- Approximately 40% of patients with trisomy 21 have cardiac malformations, which are responsible for most of the deaths in early childhood
- Serious infections are another important cause of morbidity and mortality

## Klinefelter Syndrome (KS)

This syndrome is best defined as male hypogonadism that develops when there are at least two X chromosomes and one or more Y-chromosomes. Most patients are 47, XXY. This karyotype results from the non-disjunction of sex chromosomes during meiosis.

- The extra X chromosome may be of either maternal or paternal origin.
- Advanced maternal age and a history of irradiation of either parent may contribute to the meiotic error resulting in this condition.
- Clinical features:

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- Tall statures
- Small firm testes
- Reduced facial, body, and pubic hair and Gynecomastia are also frequently noted.
- Along with the testicular atrophy, the serum testosterone levels are lower than normal and urinary Gonadotropin levels are elevated.
- KS is the most common cause of hypogonadism in males.
- KS may be present in 3 to 7% of men with breast cancer

#### **Note Three differences**

- True hermaphrodite -----XXY
- Klinefelter---47 XXY
- Partial mole----69 XXY

#### **Triplet-Repeat Mutations**

- Diseases in which the mutation is characterized by a long repeating sequence of 3 nucleotides
- · Example:
  - Huntington disease
  - Myotonic dystrophy
  - Fragile X syndrome

#### Fragile X syndrome

NAME AND ADDRESS OF TAXABLE PARTY.

- It is one of the most common causes of familial mental retardation
- They express a characteristic physical phenotype that includes a long face with a large mandible, large everted ears, and large testicles (macro-orchidism).
- The only distinctive physical abnormality that can be detected in at least 90% of postpubertal males with fragile X syndrome is macro-orchidism.

## Ehlers-Danlos Syndromes and Prader-Willi syndrome

### **Ehlers-Danlos syndromes (EDSs)**

- Ehlers-Danlos syndromes (EDSs) are characterized by defects in collagen synthesis or structure. All are single-gene disorders, but the mode of inheritance encompasses all three of the Mendelian
- \* At least six clinical and genetic variants of EDS are recognized. Because defective collagen is present in all the variants, certain clinical features are common to all.

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#### Clinical features are:

- Fragile, hyper-extensible skin vulnerable to trauma, Hypermobile joints, rupture of internal organs like colon, cornea & rupture of large arteries (common cause of sudden death)
- Wound healing is poor. The most striking feature of EDS-K is kyphoscoliosis

#### Prader-Willi syndrome

- It is characterized by mental retardation, short stature, hypotonia, obesity, small hands and feet. and hypogonadism
  - ✓ In 60% to 75% of cases, an interstitial deletion of band q12 in the long arm of chromosome 15

#### Mental Retardation



- The most common cause of chromosomal abnormality causing mental retardation is--- Down syndrome
- The most common mendelian disorder causing mental retardation is --- fragile X syndrome
- The irreversible cause of mental retardation-----thyroid deficiency-that's why thyroid hormone is necessary for fetal brain development
- The least common cause of mental retardation is Klinefelter syndrome

#### **Fetal Alcohol Syndrome**



- Fetal alcohol syndrome is a condition in a child that results from alcohol exposure during the mother's pregnancy. Fetal alcohol syndrome causes brain damage and growth problems. The problems caused by fetal alcohol syndrome vary from child to child, but defects caused by fetal alcohol syndrome are not reversible.
- Facial characteristic:
  - Thin upper lip
  - √ Short nose
  - Small eye-opening
  - Small midface
  - √ Small head circumference
  - ✓ Indistinct Philtrum

#### Radiosensitive Tumor



- Most radiosensitive cell of body Is lymphocyte
- Most radiosensitive testicular tumor is Seminoma
- Most radiosensitive ovarian tumor is Dysgerminoma
- Most radiosensitive lung tumor is Small cell carcinoma of the lung
- Most radiosensitive tumor of bone tumors are Multiple myeloma and Ewing sarcoma
- Most radiosensitive brain tumor is Medulloblastoma
- Most radiosensitive renal tumor is Wilms tumor

## **Radiation and Cell Cycle**



Genetic Disorder

- UV-C is most energetic and most harmful
- UV-A is the least energetic and least harmful.
- UV light can cause cataract which involves the cortex
- UV radiations are non-ionizing radiation
- Gamma rays has the deepest penetrating ability
- Radiation injury depend upon the duration of radiation
- Permissible radiation exposure is 7 rad/year
- The Fatal dose of total body radiation is 400 roentgen
- Radiation usually cause injury after more than 10 years
- Lead does not allow radiation to pass that's why pregnant women is advised to have a lead shield for X-ray chest
- Genetic change may occur due to exposure to lonizing radiation
- Radiation cause thyroid cancer, papillary cancer account for 90% of radiation-induced thyroid cancer
- Most common cancer in the nuclear outbreak is blood cancer (leukemia)
- The Natural sources of radiation to which most of the people are exposed are Cosmic rays and Sunlight
- Exposure of cells to radiation or chemotherapeutic agents induces DNA damage
- Radiation, whatever its source (UV rays of sunlight, x-rays, nuclear fission, radionuclides) is an established carcinogen
- Therapeutic irradiation of the head and neck can give rise to papillary thyroid cancers years later
- The Oncogenic properties of ionizing radiation are related to its mutagenic effects
- Carcinogenic influence of radiation appears after > 10 years
- Most radiosensitive phase of the cell cycle is m-phase
- The cells is vulnerable to radiation in the stage of mitosis, less so during the synthesis phase and relative insensitive during resting periods
- "S" phase is the most radio-resistant phase of cell cycle
- But "S" phase is the most chemosensitive phase of cell cycle
- Radiosensitivity of a cell also depends on its histological type and oxygenation of the tissue
- Radiation cause damage by alteration in cellular protein
- The Tumor most commonly arising after radiation----meningioma, tumor most sensitive to radiation is Seminoma

#### IMPORTANT GENES



#### Proto-oncogenes:

- ✓ Normally promote normal cell growth, mutation convert them into oncogenes, which cause cells to divide excessively
- Protoncogens is converted into oncogene by-----point mutation
- RAS is the most commonly mutated proto-oncogene in human tumors
- The RAS gene is most commonly activated by point mutations
- ✓ (Proto-oncogene-----RAS) (oncogene-----mutant RAS)

#### Oncogenes:

 Mutant versions of proto-oncogenes that function autonomously without a requirement for normal growth-promoting signals or Mutant alleles of proto-oncogenes are called

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oncogenes or oncogene are mutated protoncogens

- Virus contains viral oncogenes, and these oncogenes are capable of causing cancer, integration of viral genes into the host DNA overrules the regulatory check and balance of cellular mechanism.
- Oncogenic virus may be DNA (HPV, HSV II, EBV, hepatitis B) or RNA (Human T-cell leukemia virus I and II, human immune deficiency virus) virus
- Oncogenes activation:
  - ✓ Activation of proto-oncogenes to oncogenes results in a gain of function and may be quantitative (an increase in the production of an unaltered product) or qualitative (the production of a modified product).
  - ✓ Quantitative forms of oncogene activation occur either by amplification or by transposition to an active chromatin domain.
  - ✓ Qualitative forms of activation occur either by point mutation or by the production of a novel product from a chimeric gene. These changes are generally dominant mutations and are clonally maintained.
- Virus cause cancer by:
  - Tumor virus transforms the human cell into the cancer cell by:
    - o Introducing viral cancer---cause oncogenes into host cell DNA
    - o Causing translocation and over-expression of host protoncogens

#### ❖ P53:

- The p53, tumor suppressor gene is one of the most commonly mutated genes in human cancers
- One of the most important p53 functions is its ability to activate apoptosis and thus prevent overcrowding of mutant cell
- Mutant p53 proteins not only lose their tumor-suppressive activities but often gain additional Oncogenic functions that endow cells with growth and survival advantages.
- Mutation in P53:
  - ✓ Cause loss of function
  - Lead to continued cell division despite DNA damage
  - Lead to increased cell mutation
  - Li-Fraumeni syndrome is associated most commonly with a mutation in P53 tumor suppressor gene

### **Tumor Suppressor Genes**

Genes	Chromosome	Associated Tumor
VHL	3р	Von Hippel Lindau, Renal Cell CA
APC	5p	Familial Adenomatous polyposis, Colon CA
WT-1	11p	Wilm's tumor
Rb	13q	Retinoblastoma, Osteosarcoma
Name of disease with DNA repair defect	Fanconi anemia, Ataxia telangiectasia, bloom syndrome, Xer derma Pigmentosa	

# CELL & MEMBRANE 2 **PHYSIOLOGY**

#### Plasma membrane:

- The cell membrane is also known as the plasma membrane
- The normal thickness of plasma membrane 7-11 nanometer
- It is the Biological membrane that separates the interior of all the cells from the outside environment (the extracellular space)
- It consists of a lipid bilayer with embedded proteins.
- The Plasma membrane is chiefly made up of protein
- The plasma membrane is about 40% lipid and 60% protein
- Most of the lipids in the plasma membrane are phospholipids

#### Smooth Endoplasmic Reticulum----DSSP

- Detoxification of toxic substances like alcohol
- Store and release calcium
- · Steroid synthesis that's why more in Leydig cell because Leydig synthesis testosterone, which is also steroid
- Produce peroxisome

#### Rough Endoplasmic Reticulum (RER):

- Protein maker
- Continuous with nuclear membrane
- · Give Basophilia to cell
- Nissl bodies (RER in neurons)
- Synthesis enzyme----Acetyltransferase
- Synthesis peptide neurotransmitter
- Contain ribosome

#### Peroxisomes:

- These are formed by budding off from smooth ER
- Contain H<sub>2</sub>O<sub>2</sub> and oxidase
- Cause oxidation (detoxification) of poisons and toxins of cell
- Do beta-oxidation of long-chain fatty-acid
- Bounded by a single membrane

#### Proteasomes:

- \* Proteasomes are protein complexes, which degrade unneeded or damaged proteins by proteolysis, a chemical reaction that breaks peptide bonds.
- Enzymes that help such reactions are called proteases.

- These are organelles formed by Golgi apparatus
- On H and E staining look like Hollow structure around the nucleus
- Function:
  - Contain nucleases for degrading DNA and RNA
  - Contain hydrolytic enzyme for intracellular digestion
  - Contain bactericidal agent e.g. lysozyme (which dissolve the bacterial cell wall) and lysoferrin (which binds iron and other substances before they can promote bacterial growth), acid at a pH 5.0, which activates the hydroxylase and inactivates bacterial metabolic system
  - ✓ Responsible for regression of various tissue e.g. uterus regress to small size after childbirth
- Golgi apparatus
  - Form acrosomal cap and lysosome (Acrosome reaction is by lysosome)
  - Packing products into vesicle for transport like the binding of carbohydrate with protein so final packing occurs in Golgi apparatus

#### Mitochondria:

- These are self-replicative organelles that synthesize high energy phosphate compound
- All mitochondrial DNA is of maternal origin
- Synthesize ATPs
- Structure:
  - Two lipid bilayer membrane, outer and inner
  - Shelves formed by infolding of inner lipid bilayer membrane, onto which oxidative enzymes are attached
  - Mitochondrial cavity filled with a gel matrix, containing enzymes of the citric acid cycle and beta-oxidation etc and it also contains its own DNA
  - ✓ Cardiolipin is an important component of inner mitochondrial membrane (almost 20%) of mitochondrial lipids)
  - ✓ Electron transport chain is mainly present on the inner mitochondrial membrane

### Glycocalyx:

. The entire outer surface of the cell membrane has a carbohydrate coat called Glycocalyx

#### Nucleolus:

- . The nucleolus is nothing but just contain a large amount of RNA and protein
- It is the site of ribosomal RNA synthesis and ribosomal assembly
- Perinuclear space which is also called the Perinuclear cistern is the space or gap between the inner and outer membranes surrounding the nucleus
- · Nucleoli in the active protein synthesis, have a prominent nucleolus
- · Having no limiting membrane
- Other structure with No limiting membrane:
  - √ Ribosome
  - √ Cytoskeleton
- Double membrane bounded organelles:
  - ✓ Mitochondria
  - √ Golgi apparatus
  - ✓ Endoplasmic reticulum and Nucleus

Chapter 21

**Cell & Membrane Physiology** 

Cytoskeleton



#### Microtubules:

- Microtubules are a component of the cytoskeleton
- Microtubules are the central structural support in cilia and flagella
- Microtubules act as tracks for two class of motor protein: Kinesins and Dynein
- Kinesins:
  - Moving along microtubules usually carry cargo such as organelles and vesicles from the center of the cell to its periphery
- Dynein:
  - ✓ Important in sliding microtubules relative to one other during the beating of cilia flagella
  - Protein dynein is responsible for the bending moment of cilia and flagella
  - They carry cargo from periphery to center of the cell
  - ✓ Act as force-generating agent in positioning the muscle spindle and moving chromosome during mitosis

#### Microfilaments:

- Compared to the microtubule, microfilaments are:
  - ✓ Smaller, 7mm in diameter for microfilament
  - ✓ Not hollow like microtubules
- The thinnest class of the cytoskeletal fibers, are solid rod of the globular protein actin
- Microtubules are designed to resist tension
- Thicker filament, composed of a motor protein called myosin.
- Localized contraction also derived amoeboid movement





#### 1) Gap junction

- Cytoplasmic bridge for sharing of the small molecule between cell
- These permit the free passage between the cells of ions and small molecules
- They are cylinders constructed from 6 copies of transmembrane proteins called connexins.
- Because ions can flow through them, gap junctions permit changes in membrane potential to pass from cell to cell.
- Example:
  - ✓ Heart act as syncytium because of these gap junction
  - ✓ The action potential in heart (cardiac) muscle flows from cell to cell through the heart providing the rhythmic contraction of the heartbeat.
  - ✓ At some so-called electrical synapses in the brain, gap junctions permit the arrival of an action potential at the synaptic terminals to be transmitted across to the postsynaptic cell without the delay needed for the release of a neurotransmitter.
  - ✓ As the time of birth approaches, gap junctions between the smooth muscle cells of the uterus enable coordinated, powerful contractions to begin.

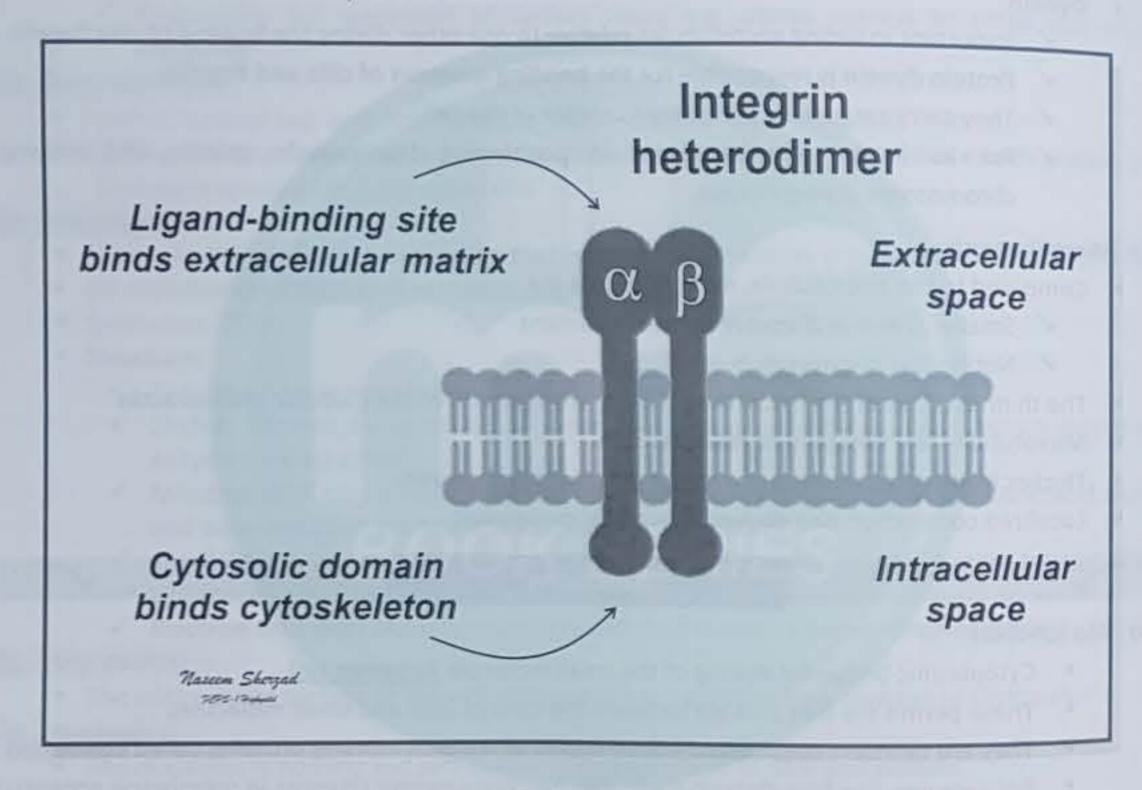
Cell & Membrane Physiology

#### 2) Tight junction:

- Tight junctions seal adjacent epithelial cells in a narrow band just beneath their apical surface. They consist of a network of claudins and other proteins.
- They limit the passage of molecules and ions through the space between cells

#### 3) Integrins:

- Join the cytoskeleton on the inside of the cell to the extracellular matrix on the outside
- Provide a transmembrane link between ECM to the cytoskeleton
- Heterodimers of alpha and beta subunits



#### Desmosome

- These junctions are small disk-shaped "spot welds" between adjacent cell
- Link two cells together

#### 5) Hemidesmosomes:

 Hemidesmosomes are adhesive junctions that <u>link cytoplasmic filaments to basal lamina</u> instead of to each other.

#### Intermediate Filament



/ Intermediate filaments are 8-10 nm in diameter

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- ✓ They constitute a population of heterogeneous filaments that include keratin, Vimentin, Desmin, glial fibrillary acidic protein, Laminin and Neurofilaments
- ✓ In general, intermediate filaments provide mechanical strength to cells. They lack polarity and do not require GTP or ATP for assembly, which occurs along the entire length of the filament

### Major classes of intermediate filaments

Protein	Location	Function
Keratin29 distinct isoforms (16 acidic, 13 neutral/basic)	Epithelial cells	Structural support and tension bearing role, enables the cell to withstand the stress caused by stretching; keratin tonofilaments are associated with desmosome and Hemidesmosomes  Keratin serves as an immunological marker for tumors arising from epithelia————Malignant neoplasms of epithelial cell origin are called carcinomas
Vimentin- containing filaments	Fibroblast, endothelial cell, chondroblasts and various mesenchymal cells	Form a cage-like structure around the nucleus, structural support for cell  Vimentin serves as an immunological marker for tumors arising from connective tissue
Desmin+ Vimentin*	Skeletal, cardiac, smooth muscle	Form a framework linking myofibrils and myofilaments  Desmin serves as an immunological marker for tumors arising from muscle
GFAP+ Vimentin*	Astrocytes, Oligodendryocytes Schwann cells, neurons	Provide structural support.  GFAP serves as immunological marker for tumors arising from glia
Neurofilaments		Provide support for axons and dendrites  Neurofilaments serve as an immunological markers for tumors of neuronal origin  they may copolymerize with it; they are

<sup>\*</sup>Desmin GFAP are shown with Vimentin because they may copolymerize with it, they are categorized as Vimentin-like filaments

Cell & Membrane Physiology

#### 1) Active transport:

- · Require energy
- · Against the gradient---low to high
  - Primary active transport
    - · Direct energy
    - Examples:
      - √ Na-K<sup>\*</sup> ATPase
      - ✓ H\*-K\* ATPase
      - √ Ca<sup>+</sup> ATPase
  - Secondary active transport
    - Indirect energy
    - Types with example
      - ✓ Co-transport or symport (2 in the same direction):
        - o The other molecule is moved with sodium
        - o Example: Glucose-Na cotransport in kidney and intestine
      - ✓ Counter-transport or antiport (two in opposite direction):
        - o The other molecule is moved in the opposite direction of sodium
        - o Examples: Na-Ca transport, Na-H transport

#### 2) Passive transport

- Toward electrochemical gradient
- Downhill
- No energy required
- Types

#### · Simple Diffusion

- Not carrier mediated
- Not saturable
- · Not depend on the magnetic field
- Not exhibits specificity
- Inversely proportion to the thickness of the membrane
- Depend on the concentration of gradients
- No V<sub>max</sub>
- Examples
  - ✓ Gases and non-polar molecule

#### · Facilitated diffusion

- Occur Via ion channels/carrier protein
- Exhibit specificity
- Having V<sub>max</sub>
- Faster than Simple Diffusion
- Examples:
  - ✓ Glucose transport in muscle and adipose tissue
  - √ Fructose absorption

Osmosis and Osmolarity Diffusion of water from higher conc. to lower conc. i.e. from dilute solution to concentrated

solution through a semi-permeable membrane is called osmosis

Osmotic pressure:

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- ✓ The Pressure required to stop osmosis is called osmotic pressure.
- Osmotic pressure depends upon the number of particles per unit volume concentration
- While calculating plasma Osmolarity Na\* is multiplied by two anion
- Oncotic pressure: Oncotic pressure is the contribution made to total Osmolarity by collides
- Osmole: No of particles in one mole of undissociated solute is called one Osmole
- Osmolarity: Osmole per liter of solution is called Osmolarity, Osmolarity increase with the increase in No. of solute particles
- Endocytosis:
  - The Process by which a large molecule enters a cell
  - The membrane protein clathrin is involved in receptor-mediated Endocytosis
  - Types of Endocytosis:
    - Pinocytosis: engulfing a liquid (cell drinking)
    - Phagocytosis: engulfing another cell or organic matter (cell eating)
- Exocytosis: Opposite of Endocytosis, cell remove of material

- · Albumin is the most abundant of the plasma proteins
- Albumin is responsible for 75 to 80% of the osmotic pressure of human plasma due to its low molecular weight and high concentration. Albumin acts as cotransport for fatty acid
- Acid drugs bind with Albumin and Basic drug bind with alpha glycoprotein
- · Albumin is normally absent in the urine
- Serum Albumin concentration falls gradually from early pregnancy and this is related to ECF expansion
- \* It is the most frequently used serum protein as an indicator of nutritional status. Pre-operative albumin levels are better prognostic indicator than anthropometric measurements for morbidity and mortality in surgical patient

### Positive and Negative Feedback Mechanism

#### 2) Positive feedback mechanism:

- Output exaggerate the original stimulus
- Positive feedback is also called a vicious circle, because it is defective and fails to save a life, and once started lead to death.
- Example of the positive feedback mechanism
  - ✓ Blood clotting
  - ✓ Childbirth
  - ✓ LH surge
  - ✓ The action of oxytocin on uterine muscle during the child-birth

#### 6) Negative feedback mechanism

- When the final result is opposite to initial stimulus, it is called the negative feedback mechanism
- The most human system achieves homeostasis by Negative feedback mechanism. Body temperature, blood glucose level, Blood PH, Blood pressure, Hormone level, Oxygen and Carbon-dioxide level, water and electrolyte balance etc. are all controlled by negative feedback. Other imp examples: Baroreceptor reflex, Renshaw cell

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NASEEM SHERZAD FCPS -1 HIGH-YIELD

#### Cell Cycle



The key processes in the proliferation of cells are DNA replication and mitosis. The sequence of events that control these two processes is known as the cell cycle.

#### **Proliferative Capacities of Tissues**

The ability of tissues to repair themselves is critically influenced by their intrinsic proliferative capacity. Based on this criterion, the tissues of the body are divided into three groups.

#### Permanent:

- Remain in GO, can't enter the cell cycle, once they are destroyed they can't be regenerated
- Non-dividing cell
- \* Example: lens, muscles (skeletal and cardiac muscle), neuron and RBC
- Only hypertrophy or atrophy can occur (no hyperplasia)
- Lens> skeletal muscle> Neuron (olfactory Nerve-----Only neuron that can regenerate, replaced by stem cell

#### Stable:

- Enter G1 from G0 when stimulated
- it is Stable tissue
- Hepatocyte and lymphocyte
- Can undergo hypertrophy/hyperplasia

#### Labile:

- Never go G0, divide rapidly with a short G1
- Continuously dividing cell, constantly multiply throughout life
- Bone marrow, gut epithelium, skin epithelium, hair follicle and germ cell
- . Chemotherapy tries to inhibit S and M phase which effect labile cell
- In the dividing cell, spindles are formed by tubulin

#### **Skeletal Muscles**

- There are more than 640 skeletal muscles in the adult human body.
- In skeletal muscle the muscle fibers are grouped into bundles called fascicule
- Because of its large mass and the fact that skeletal muscles receive 25% of the cardiac output at rest, sympathetically mediated vasoconstriction in vessels supplying this tissue allows central hemodynamic variables (e.g., blood pressure) to be spared during stresses such as Hypovolemic shock.
- Endomysium: individuals muscle fiber are surrounded by a thin layer of supporting tissue called
   Endomysium
- Perimysium: The fascicule are separated from each other by a layer of supporting tissue called
   Perimysium
- Epimysium: The whole muscle is invested by a dense sheath of supporting tissue called Epimysium
- Parts of skeletal muscle:
  - ✓ Origin: attachment to the stationary end of the muscle
  - ✓ Belly: thicker, flesh in entire length and it is the middle region of muscle.
  - ✓ Insertion: attachment to the mobile end of the muscle

#### Skeletal muscle Cardiac muscle Smooth muscle Striated Striated Non-striated Muscle fibers are Single centrally placed Single central nucleus Multinucleated nucleus Contain Ca2+-Troponin C Contain Ca2+ - Troponin C Ca2+ - Calmodulin Contain T-tubules Contain T-tubules Lack T-tubules No myofibrils in smooth muscle

#### **Types of Muscle Fibers**

Type 1 Muscle	Type 2 Muscle	
■ Slow-twitch, red fibers resulting from:  ✓ Increase mitochondria and Myoglobin concentration (increase oxidative phosphorylation) sustained contraction	<ul> <li>Fast-twitch, white fibers resulting from:</li> <li>✓ Decrease mitochondria and Myoglobin concentration (increase anaerobic Glycolysis)</li> <li>Weight training results in hypertrophy of fast-twitch muscle fibers</li> </ul>	

#### **Action Potential**

- Resting membrane potential is generated or achieved by-------K<sup>+</sup> efflux
- Resting membrane potential is maintained by————Na<sup>+</sup>-K<sup>+</sup> ATPase pump
- Resting membrane potential (RMP)-----(-90 mV)
- Most diffusible ion in excitable tissue is-----Cl
- Plateau of the action potential is due to-----Ca<sup>++</sup> influx
- The action potential is propagated due to depolarization
- Speed of action potential through large nerve fiber--------30 m/s
- The compound muscle action potential or compound motor action potential is an electromyography investigation. The CMAP idealizes the summation of a group of almost simultaneous action potentials from several muscle fibers in the same area. These are usually evoked by stimulation of the motor nerve.
- Human axon growth rates can reach 1 mm/day in small nerves and 5 mm/day in large nerves.
- \* The Tropic function of nervous tissue:
  - ✓ Denervation of muscle or gland leads to its atrophy
  - ✓ Reinnervation restore its structure and function

Labeled line

Principle

### Cell & Membrane Physiology

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## Inhibitory Postsynaptic Potentials (IPSP)

- Caused by the flow of negatively-charged ion
- The IPSP is caused by the flow of negatively-charged chloride ions into the postsynaptic neuron.
- The inhibitory neurons secrete the inhibitory neurotransmitters to the synapses.
- The most common inhibitory neurotransmitters are glycine and GABA.
- A Hyperpolarization

0000

### Excitatory Postsynaptic Potentials (EPSP)

- Caused by the flow of positively-charged ion
- A depolarization

THE RESERVE AND PERSONS NAMED IN COLUMN 1985

- The EPSP is caused by the binding of the excitatory neurotransmitters, which are released from the presynaptic membrane.
- The main excitatory neurotransmitter is glutamate.

#### All or none principle

- · According to all or none principle, if stimulus reaches the threshold, the action potential is always the same. A stronger impulse will not cause a larger impulse
- If the stimulus is too small (sub-threshold)------No action potential
- If the stimulus is larger than the threshold (supra-threshold)------Same size action potential as above
- "All or none" principle occur at the axon hillock

#### Temporal & Spatial Summation

- Summation may be temporal or spatial. Temporal summation occurs if repeated afferent stimuli cause new EPSPs before previous EPSPs have decayed. A longer time constant for the EPSP allows for a greater opportunity for summation. When the activity is present in more than one synaptic knob at the same time, spatial summation occurs and activity in one synaptic knob summates with activity in another to approach the firing level. The EPSP is therefore not an all-or-none response but is proportionate in size to the strength of the afferent stimulus.
- Spatial summation of IPSPs also occurs, as shown by the increasing size of the response, as the strength of an inhibitory afferent volley is increased. Temporal summation of IPSPs also occurs.
- Occlusion phenomena: The phenomena occlusion will be, that the quantity of excited neurons at simultaneous irritation afferent of both nervous centers appears less than the arithmetic sum of excited neurons at separate irritation of every one afferent an input separately E.g. the stimulation of motor unite -A causes contraction of 120 muscle fibers and stimulation of motor unite-B cause contraction of 60 fibers. When they are stimulated together, contraction of 120 fibers occurs that's why this phenomena occlusion result in decrease in force of expected total response

Terms Definition It increases the resting potential across the myocytes i.e. the cell membrane becomes more negative and less sensitive to excitation, so decrease neuronal excitability in RMP and nerve stimulation difficult to Hypokalemia create. Neuron becomes hyperpolarized Hyperkalemia Neuron becomes more excitable Decrease in height of action potential Hyponatremia Hypercalcemia Decrease the excitability of the nerve Hypocalcemia Increase the excitability of the nerve Tetrodotoxin is a sodium channel blocker. It inhibits the firing of action potentials in neurons by binding to the voltage-gated sodium channels in nerve cell membranes and blocking the passage of sodium ions Tetrodotoxin (responsible for the rising phase of an action potential) into the neuron. Blocking Na+ during the action potential Change of RMP from -90 mV to 0 and then overshot to +35 mV is called Depolarization depolarization. It is due to Na influx. Repolarization——change of membrane potential from +35 mV to Repolarization again -90 mV (RMP) is called Repolarization. It is due to K efflux Voltage-gated K\* channels remain open after the action potential reach resting level Hyperpolarization is a change in a cell's membrane potential that makes Hyperpolarization it more negative. It is the opposite of a depolarization. Hyperpolarization

#### Regulation of Na-K ATPase

sight, sound and so forth is called a modality of sensation

Each of Principle type of sensation that we can experience -Pain, touch,

The specificity of nerve fibers for transmitting only one modality of

is often caused by efflux of Kt or influx of CI

sensation is called the labeled line Principle

- The amount of Na<sup>+</sup> normally found in cells is not enough to saturate the pump, so if the Na<sup>+</sup> increases, more are pumped out. Pump activity is affected by second messenger molecules (e.g. cAMP, diacylglycerol)
- The magnitude and direction of the altered pump effects vary with experimental conditions.
- Thyroid hormones increase pump activity by a genomic action to increase the formation of Na, K ATPase molecules. Aldosterone also increase the number of pumps, although the effects is probably secondary
- Dopamine in the kidney inhibits the pump by phosphorylating it, causing a natriuresis
- Insulin increases pump activity, probably by a variety of different mechanism

#### Site of functional communication between two neurons is called synapses

- . Mechanism:

  - ✓ Ca<sup>++</sup> is most important for the release of neurotransmitter
- The Factor that increases synaptic transmission
  - ✓ Alkalosis

    —increases neuronal excitability
  - ✓ Caffeine
  - ✓ Theophylline
  - ✓ Strychnine
- The Factor that decreases synaptic transmission
  - ✓ Acidosis
  - √ Hypoxia
  - ✓ Anesthesia

#### Neuromuscular junction

- It is the synapse between the axon of motorneurons and skeletal muscle
- Synaptic cleft: Space between the nerve terminal and muscle membrane
- ❖ Endplate: An average human endplate contains about 15 to 40 million acetylcholine receptors. Each nerve impulse releases about 60 acetylcholine vesicles, and each vesicle contains about 10,000 molecules of the neurotransmitter. This amount is enough to activate about 10 times the number of acetylcholine receptors needed to produce a full end plate potential. Therefore, a propagated response in the muscle is regularly produced, and this large response obscures the end plate potential. However, the end plate potential can be seen if the tenfold safety factor is overcome and the potential is reduced to a size that is insufficient to fire the adjacent muscle membrane. This can be accomplished by administration of small doses of curare, a drug that competes with acetylcholine for binding to muscle-type nicotinic acetylcholine receptors. The response is then recorded only at the end plate region and decreases exponentially away from it. Under these conditions, end plate potentials can be shown to undergo temporal summation.

#### Presynaptic terminals:

- · Neurotransmitter released from the presynaptic terminal is acetylcholine
- Acetylcholine is stored in synaptic vesical with ATP and proteoglycan for later release
- Botulinum toxin:
  - ✓ Block release of Ach from presynaptic terminal
  - ✓ Botulinum toxin from the anaerobic bacillus Clostridium botulinum decreases the release.

of ACh from neuronal vesicles. It binds selectively to a receptor on the presynaptic membrane of cholinergic nerve terminals and is endocytosed inside synaptic vesicles responsible for re-uptake of neurotransmitter.

- ✓ Inside the cell, botulinum toxin is released into the cytosol, where it cleaves cytoplasmic synaptosomal-associated protein 25 (SNAP-25) on the cell membrane, a protein that is essential for docking and fusion of vesicles with the neuronal membrane.
- ✓ Therefore, botulinum toxin inhibits neurotransmitter release.
- \* Hemicholinium, Block reuptake of Choline into presynaptic
- Decrease extracellular calcium or Hypermagnesemia reduce the release of acetylcholine release from presynaptic vesical

#### Postsynaptic terminal:

- The postsynaptic terminal contain nicotinic receptors
- Curare, Competes with Ach for receptors on the motor endplate

#### Synaptic vesicles:

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- Synaptic vesicles are small, membrane-bounded structure in the axoplasm of the transmitting membrane
- They are discharging neurotransmitter into the synaptic cleft by exocytosis, they don't manufacture it.

#### · Quantal Release of Transmitter:

• Small quanta (packets) of acetylcholine are released randomly from the nerve cell membrane at rest. Each produces a minute depolarizing spike called a miniature endplate potential, which is about 0.5 mV in amplitude. The size of the quanta of acetylcholine released in this way varies directly with the Ca<sup>2+</sup> concentration and inversely with the Mg<sup>2+</sup> concentration at the end plate. When a nerve impulse reaches the ending, the number of quanta released increases by several orders of magnitude, and the result is the large end plate potential that exceeds the firing level of the muscle fiber.

#### . Enzymes:

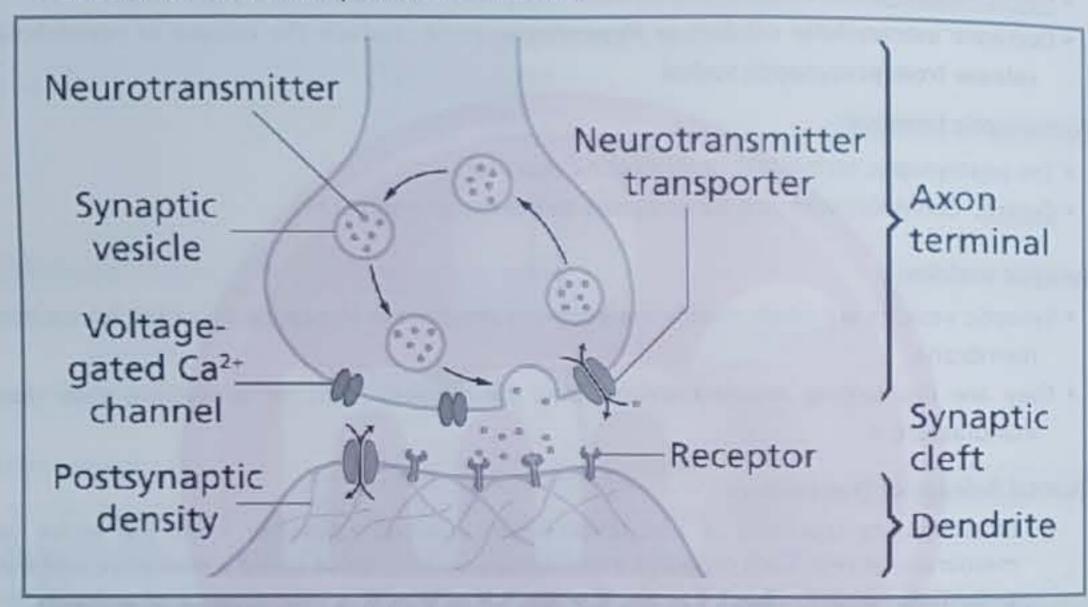
- \* Choline acetyltransferase:
  - ✓ Catalyze the formation of acetylcholine from: acetyl-coenzyme A and Choline
- Acetylcholinesterase enzyme:
  - ✓ Terminate the action of acetylcholine by the process of hydrolysis to: acetate and Choline
  - ✓ Inhibitor of acetyl cholinesterase include:
    - Neostigmine----cant cross BBB, <u>Doc for myasthenia gravis</u>
    - o Rivastigmine
    - o Physostigmine----can cross BBB
    - o Pyridostigmine
    - o Donepezil----use for Alzheimer disease
    - Edrophonium is a readily reversible Acetylcholinesterase inhibitor.

Cell & Membrane Physiology

 Edrophonium (by the so-called Tensilon test) is used to differentiate myasthenia gravis from cholinergic crisis and Lambert-Eaton syndrome (common side effect of edrophonium is nausea)

#### Ach like drugs:

- Methacholine
- · Carbachol-mainly for eye
- \* Nicotine
- . Bethanecol-used mainly for GIT and Bladder

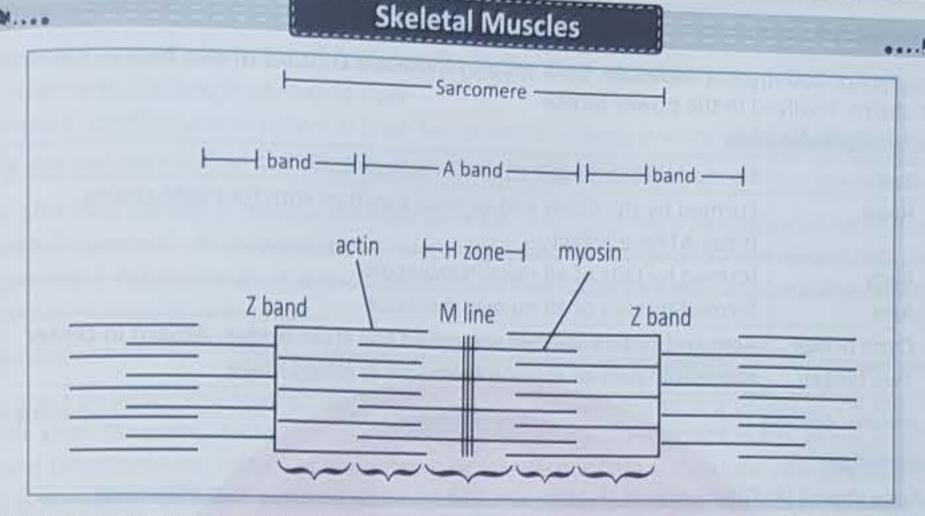


#### **Naseem Sherzad High-Yield Points**

- The nucleus basalis, also called nucleus basalis of Meynert is a group of neurons in the substantia innominata of the basal forebrain, which has wide projections to the neocortex and is rich in acetylcholine and choline acetyltransferase.
- Mushroom poisoning—treatment is atropine
- Atropine poisoning——— treatment is pyridostigmine
- Organophosphorus poisoning: treatment is Pralidoxime (cause reactivation of Acetylcholinesterase) and atropine
- Atropine is a prototype drug of parasympatholytics, causes the reversible block of cholinoceptors.
- A Prolonged neuromuscular block occurs when suxamethonium is given after neostigmine

#### Thermal changes during muscle contractions

- Resting heat: Resting heat is the heat generated when the muscle at rest i.e. not contracting
- Initial heat refers to the heat generated in excess of resting heat during muscular contraction



- Skeletal muscle fiber: Structural and functional unit of muscle is called a muscle fiber
- Composition:
  - ✓ Sarcolemma: it is the cell membrane of muscle fibers that surround it
  - ✓ Sarcoplasm: it is matrix present in muscle fiber
  - ✓ Sarcoplasmic reticulum:
    - It contains a protein called "Calsequestrin". Which can bind up to 40 times more Ca<sup>++</sup> and hold the calcium after muscle contraction
    - Sarcoplasmic reticulum containing large amount of Ca<sup>+</sup>
  - ✓ Myofibrils: Each myofibrils is innervated by one nerve ending

#### Myofibrils

Each muscle fiber contains in its Sarcoplasm hundreds of myofibril

#### · Each myöfibril contains:

- √ 1500 myosin(thick) filament
- ✓ 3000 Actin (thin) filament

#### Structural peculiarities:

Actin and myosin filaments partly interdigitated causing alternate dark and light band

- ✓ I Band: light band containing only Actin filament. Isotropic to polarized light
- ✓ A band: Dark band containing Actin and myosin filaments where they overlap.

  Anisotropic to polarized light
- ✓ H zone: light area in the center of A band. Seen when the muscle is stretched beyond its resting length due to pulling apart of Actin filaments
- ✓ M line: dark line in the center of H-zone

#### \* Z-disc

- ✓ It is a disc (plate) of filamentous protein to which Actin filament is attached.
- ✓ Function: Z-disc pass from myofibrils to myofibrils and attach them together

#### Sarcomere:

- ✓ The Portion of myofibril between two successive Z-disc is called a sarcomere
- ✓ Smallest contractile unit (functional unit) of a muscle fiber

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Cell & Membrane Physiology

Name and Address of the Owner, where

#### Myosin filaments

- \* It consists of 200-myosin molecule. Each myosin molecule consists of two heavy chains and four light chains. Involved in the power stroke
- Structural peculiarities:

Tail	Formed by two heavy chains, which coiled into a helix
Head	Formed by the other end of helix together with four light chains.  It has ATPase activity
Body	formed by tails of all myosin molecule
Arm	formed by tails of all myosin molecule
Cross bridge	Arm and head together are called the cross bridge. Absent in center
Two hinges	Moveable part of myosin filaments is called hinge

#### Actin filament

#### Composed of:

- . F-Actin strand (F=Filamentous), F-actin can also be described as a microfilament
  - ✓ Two F-Actin strands are wound into a helix
  - ✓ Each strand of F-Actin molecule is made by polymerization of G-Actin protein molecule.
  - Each G-actin molecule has one ADP that is an active site, which interacts with cross bridge causing sliding process

#### Tropomyosin strand

- Two strands of tropomyosin are coiled into a helix that is attached to F-Actin strand
- Function: In Resting-state tropomyosin strand physically, cover the active site of F-Actin strand, Preventing muscle contraction. Tropomyosin acting as a "relaxing protein" at rest by covering up the sites where myosin binds to actin.

#### Troponin complex

It is attached 2/3 distance along each tropomyosin molecule

- ✓ Troponin I----To attach with Actin
- Troponin T----To attach with tropomyosin
- Troponin C------- To attach with Catt

#### Titin

- Titin is the largest known protein
- Stabilize position of contractile filaments
- Functions as a molecular spring, which is responsible for the passive elasticity of muscle.
- . It connects the Z line to the M line in the sarcomere
- Titin is the third most abundant protein in the muscle (after myosin and actin), and an adult human contains approximately 0.5 kg of Titin.
- Returned to the relaxed position
- Differences:
  - ✓ Titin is the largest known protein
  - ✓ Actin is the most abundant protein in most eukaryotic cells.
  - ✓ Collagen is the most abundant protein in the body, making 25-35% of all the whole-body proteins
  - ✓ Dystrophin gene (DMD), is the longest known human gene, provides instructions for making a protein called dystrophin.

#### Transverse tubules

- . These are inward extension of Sarcolemma in the form of penetrating tubules in the direction transverse to the length of muscle fiber
- Function: conduct action potential from Sarcolemma to deep interior of muscle fiber

### Activation of Actin filament by

Action potential spread in muscle membrane-→ Ca<sup>++</sup> released from Sarcoplasmic reticulum → Ca<sup>++</sup> bind with Troponin C → conformation change → pushes tropomyosin strand deeper into the groove between two F-Actin strands → active site (ADP) on F-Actin uncovered → interaction between Actin and myosin -> muscle contraction

#### The Contraction will produce the following

The process by which the contraction of the muscle is brought about is a sliding of the thin filaments over the thick filaments. Note that this shortening is not due to changes in the actual lengths of the thick and thin filaments, rather, by their increased overlap within the muscle cell. The width of the A bands is constant, whereas the Z lines move closer together when the muscle contracts and farther apart when it relaxes

- A-band -----No change in length
- \* I-band-----Shortens
- \* H-zone (light area in the center of A band)-----Shortens

#### **Summation of Contractions**

- The electrical response of a muscle fiber to repeated stimulation is like that of nerve.
- . The fiber is electrically refractory only during the rising phase and part of the falling phase of the spike potential. At this time, the contraction initiated by the first stimulus is just beginning
- . However, because the contractile mechanism does not have a refractory period, repeated stimulation before relaxation has occurred produces additional activation of the contractile elements and a response that is added to the contraction already present. This phenomenon is known as the summation of contractions.
- \* The tension developed during summation is considerably greater than that during the single muscle twitch. With rapidly repeated stimulation, activation of the contractile mechanism occurs repeatedly before any relaxation has occurred, and the individual responses fuse into one continuous contraction. Such a response is called a tetanus (tetanic contraction).
- It is a complete tetanus when no relaxation occurs between stimuli and an incomplete tetanus when periods of incomplete relaxation take place between the summated stimuli.

#### Motor Unite

- Composed of one motor neuron and all the muscle fibers that it innervate
- \* The number of fiber innervated by single motor neuron varies
- When a motor neurons is activated, all muscle fibers in its motor unite contract
- \* The muscle that act on the largest body mass (i.e. thigh muscles) have more motor unite that contain more muscle fibers, whereas smaller muscle (extraocular---: <10 muscle fiber per motor neuron) contain fewer muscle fibers in each motor unite
- Innervation ratio is: motor neuron: muscle fibers, vary from 1:100 to 1:2000

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PRINCIPAL PRINCI

#### Rigor

- \* When muscle fibers are completely depleted of ATP and phosphorylcreatine, they develop a state of rigidity called rigor.
- . When this occurs after death, the condition is called rigor mortis.
- In rigor, almost all of the myosin heads attach to actin but in an abnormal, fixed, and resistant

#### Effects of Denervation

- In the intact animal or human, healthy skeletal muscle does not contract except in response to stimulation of its motor nerve supply.
- . Destruction of this nerve supply causes muscle atrophy.
- . It also leads to abnormal excitability of the muscle and increases its sensitivity to circulating acetylcholine (Denervation hypersensitivity).
- Fine, irregular contractions of individual fibers (fibrillation) appear. This is the classic picture of a lower motor neuron lesion. If the motor nerve regenerates, the fibrillations disappear. Usually, the contractions are not visible grossly, and they should not be confused with fasciculations, which are jerky, visible contractions of groups of muscle fibers that occur as a result of pathologic discharge of spinal motor neurons.

#### The Strength of Skeletal Muscles

- Human skeletal muscle can exert 3 to 4 kg of tension per square centimeter of cross-sectional area. This figure is about the same as that obtained in a variety of experimental animals and seems to be constant for mammalian species. Because many of the muscles in humans have a relatively large cross-sectional area, the tension they can develop is quite large.
- \* The gastrocnemius, for example, not only supports the weight of the whole body during climbing but resists a force several times this great when the foot hits the ground during running or jumping.
- An even more striking example is the gluteus maximus, which can exert a tension of 1200 kg. The total tension that could be developed if all muscles in the body of an adult man pulled together is approximately 22,000 kg (nearly 25 tons).

#### Myogenesis

Three different types of muscle form in the body.

- \* Skeletal muscle cells originate from the Paraxial mesoderm, forming somites, then dermomyotome and finally the myotome. Myoblasts undergo frequent divisions and coalesce with the formation of a multinucleated, syncytial muscle fiber or myotube. The nuclei of the myotube are still located centrally in the muscle fiber. In the course of the synthesis of the myofilaments/myofibrils, the nuclei are gradually displaced to the periphery of the cell.
- . Cardiac muscle cells originate from the prechordal splanchnic mesoderm.
- \* Smooth muscle cells originate from undifferentiated mesenchymal cells. These cells differentiate first into mitotically active cells, myoblasts, which contain a few myofilaments. Myoblasts give rise to the cells which will differentiate into mature smooth muscle cells.
- Note: The skeletal system develops from mesenchyme originated from the mesodermal germ layer and neural crest. (Only the bold and underlined words are important)

# C H A P T E RIMMUNOLOGY

### Immunoglobulin Isotypes

#### 1) IgG:

- Most abundant class in serum
- Cross placenta and provide natural immunity to fetus and neonate at birth
- Act against bacteria and virus by opsonizing
- Activate complement by classic pathway
- 4 IgG subclass, the serum concentration of IgG-1 subclass is highest (60-70%)
- Protect the body fluid
- Lowest carbohydrate

#### 2) IgA:

- Most IgA produced in the submucosa
- IgA inhibits binding of adhesive substances to the mucosal surface
- Protect the body surface
- Present in colostrum, breast milk, saliva, tear, mucus of respiratory tract digestive tract and genitourinary tract
- In serum exist as a monomer, in external secretion exist as a dimer
- Activate complement by the alternate pathway

#### 3) IgM:

- Protect the bloodstream
- The Earliest immunoglobulin to be synthesized by fetus. The only way to identify a neonatal infection serologically is by detection of pathogens specific IgM antibodies. This is because the fetus receives IgG antibodies from the mother by active transport across the placenta
- IgM is by far largest antibody in the human circulatory system
- IgM is present on B cells and its main function apparently is the control of B-cell activation
- Its pentameric structure gives it 10 free antigen-binding sites as well as it possesses a high avidity.

#### 4) IgE:

- Mediate type 1 hypersensitivity reaction
- IgE protect against the Parastic worm
- Highest carbohydrate
- IgE is bound to mast cell and basophils cell

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TOTAL VILLE

#### **Hypersensitivity Disorder**



#### Type I

- · Antibody: IgE
- Response time: 15-30 min
- Free antigen cross-links IgE on pre-sensitized mast cells and basophils, triggering the release of vasoactive amines that act at post-capillary venules (i.e. histamine). Reaction develops rapidly after antigen exposure because of preformed antibody
- Examples:
  - ✓ Anaphylaxis like some bee sting, some food/drug allergies, iodinated contrast media, Beta-lactam antibiotics (e.g. penicillin) and hymenoptera stings
  - ✓ Allergic and atopic disorder (e.g. Rhinitis, Hay fever eczema, Hives, Asthma)

#### W Type II:

- Response time: Minutes to hours
- Cytotoxic (Antibody-mediated)----------IgM, IgG bind fixed antigen on "enemy" cell, leading to cell destruction
- \* 3 Mechanism:
  - ✓ Opsonization leading to phagocytosis or complement activation
  - ✓ Complement mediated lysis
  - ✓ Antibody-dependent cell-mediated cytotoxicity, usually due to NK cells
- Examples:
  - ✓ Good pasture syndrome
  - ✓ Myasthenia Gravis and Graves' disease
  - ✓ Rheumatic fever
  - ✓ Type II diabetes mellitus
  - ✓ Bullous Pemphigoid and pemphigous Vulgaris
  - ✓ All blood disease: ITP, Pernicious anemia, autoimmune hemolytic anemia, erythroblastosis fetalis and Aplastic anemia etc.

#### Type III:

- · Antibody: IgG, IgM
- Response time: 3-8 Hours
- Immune complex antigen-antibody complex activate complement, which attracts neutrophil, neutrophil release lysosomal enzymes
- Examples:
  - ✓ Post streptococcal glomerulonephritis
  - ✓ Hypersensitivity pneumonitis, farmer's lung disease
  - ✓ SLE
  - ✓ Polyarteritis nodosa
  - ✓ Serum sickness and Arthus reaction

#### Type IV

- Main cells are T-cells and macrophages
- Response time: 48-72 hours
- Delayed cell-mediated hypersensitivity reaction
- The Response is delayed and does not involve antibody
- Example

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Immunology

- ✓ Hashimoto thyroiditis
- ✓ Rheumatoid arthritis
- ✓ Multiple sclerosis
- ✓ Guillain-Barre syndrome
- ✓ PPD and contact dermatitis (poison, Ivy, nickel allergy)
- ✓ Mantoux test, Scabies
- Chemical accelerators used in the glove manufacturing process of both latex and synthetic gloves.

	ABCD
Type-I	Allergic, Anaphylaxis and Atopy
Type-II	Anti-Body
Type-III	Immune Complex, Cytotoxic
Type-IV	Delayed

MHCI	MHCII		
HLA-A, HLA-B, HLA-C	HLA-DR, HLA-DP, HLA-DQ		
Binds TCR and CD8	Bind TCR and CD4		
Expressed on all nucleated cell, not expressed on RBC	Expressed only on antigen-presenting cells (APCs)		
The Antigen is loaded in RER with mostly intracellular peptide	The Antigen is loaded following release of invariant chains in an acidified endosome		
Mediates viral immunity	Mnemonic: 1 x 8= 8MHC 1 X CD8		
Pairs with $\beta 2$ -microglobulin (aids in transport to the cell surface)	2 x 4= 8MHC II X CD4		

B-Lymphocyte	T-Lymphocyte
B-lymphocyte secret immunoglobulin	T-cell may be helper cell
B-cell antigen can be secreted	T-cell receptors are always cell     bounded
B-lymphocyte are generated and mature in the  Bone marrow	T-lymphocyte undergo maturation in the Thymus
B-cell recognize unprocessed antigens	<ul> <li>T-cell recognize cell-bounded peptides</li> </ul>
<ul> <li>The B-cell signal transduction is Ig-α, Ig-β, CD19,</li> <li>CD21</li> </ul>	The T-cell signal transduction complex is CD3
Natural killer c	ells (NK)
* *** "	

NK cell are large granular lymphocyte

NK cells kill tumor or virus-infected target cells

#### Vaccine

- All vaccine are given intra-muscular Except:
  - MMR= subcutaneously
  - BCG= intra-dermaly
  - · Polio= oral
- All vaccine are given 0.5 ml Except:
  - BCG= 0.05 ml
  - Polio= two drops
- . In children who have not vaccinated during infancy and are still below the age of 5 years, vaccine are as follow:
  - BCG= once
  - DT and Polio Drop: 2 doses at 6 weeks interval and first booster 6 months later.
- ❖ Influenza vaccine and yellow fever vaccine contain egg protein so they are contraindicated in egg allergy people.
- If convulsion occurs within 72 hours of DPT injection further administration of pertussis vaccine is contraindicated. Then give DT alone
  - After 2 years of age, children should not receive the pertussis vaccine.
- In the event of epidemics or high risk, the measles vaccine can be given at 6 months of age.
- Immunization should be delayed only in case of illness with high-grade fever, so that any sign of the illness will not be attributed to the vaccination.
- Live vaccine should not be administered to children with immune-deficiency disease
- Meningococcal, pneumococcal and H.influenzae type-b vaccine are polysaccharide vaccines.
- \* Maternal antibodies, which are transported through the placenta, protect the infants up to the age of 3-4 months.
- Antibodies against measles persist up to 6-9 months of age, if the mother has been vaccinated or suffered from measles. Therefore, measles vaccination in children should be started after that age.
- . Contraindication to the measles vaccine includes anaphylactic reaction to neomycin, anaphylactic reaction to gelatin, pregnancy, known immunodeficiency and long-term immune-suppressive therapy.
- Transfer of maternal antibodies via the placenta is an example of passive immunization.
- Intravenous Immune Globulin (IVIG) is a human blood product consisting of antibodies, which are used to treat immunodeficiency disorders, B-cell chronic lymphocytic leukemia, inflammatory demyelinating disorders.
- . Live attenuated vaccine: BOY Love The CRIME
  - BCG, OPV, Yellow fever---- Love means Live attenuated Vaccine
  - Typhoid oral
  - Chicken Pox
  - Rubella
  - Influenza
  - Measles, Mumps
  - Epidemic typhus
- POLIO vaccine:
  - There are two types of polio vaccine, oral (Sabin) an injectable (Salk) vaccine and both contain

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Immunology

all three strains. OPV which is used in EPI is bivalent

 Even if the child has suffered from poliomyelitis, he should be vaccinated to protect him against other two types of poliovirus and also for herd immunity

#### Rotavirus vaccine:

- Rotavirus vaccine is a vaccine used to protect against rotavirus infections. These viruses are the leading cause of severe diarrhea among young children.
- It is now included in the EPI schedule as a 10<sup>th</sup> vaccine.
- Administered in two oral doses for children of 6 weeks as well as 10 weeks of age, it will help reduce the diarrhea related mortality in children below five.
- The interval between the two doses at least 4 weeks.
- The first dose of ROTAVIRUS VACCINE cannot be given if the child is older than 16 weeks of age
- There is also a small risk of INTUSSUSCEPTION from ROTAVIRUS vaccination, usually within a week after the first or second dose.

#### **Immunity**

#### Innate immunity:

#### Classification of immunity

- It is natural "general" resistance of the body to invading bacteria and toxins e.g. innate immunity resist paralytic virus infection
- Mechanism
  - ✓ Skin: resist invading bacteria and toxins
  - Stomach: Acid destroys and enzyme digest organisms swallowed with food
  - Blood: WBC (neutrophil) phagocytize invading organism
  - ✓ Tissue: tissue macrophages phagocytize invading organism

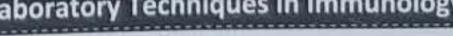
#### Acquired immunity:

- It is "specific" resistance of the body to invading bacteria and toxins
- Types: Two
  - ✓ Humoral immunity: it is due to antibodies against specific bacteria and toxins
  - Cell-mediated immunity: it is due to activated T-lymphocyte or sensitized T-cells against specific bacteria and toxins

#### Passive immunity

♦ It is temporary immunity achieved by transfusion of "antibodies or sensitized T-cells" into the person

### Laboratory Techniques in Immunology



- Direct combs test: detect antibodies bounded to RBC
- Indirect combs test: detect the production of anti-RBC antibodies Direct fluorescent antibody test (DFA): DFA identifies Ag in tissues
- \* ELISA ad RIA: extremely sensitive, ELISA is a screening test for HIV
- Western blot is a confirmatory test for HIV
- Multiple washing technique is used in Elisa
- Flow cytometry analyzes cell populations in a complex mixture
- \* CD: The cluster of differentiation (also known as cluster of designation or classification determinant and often abbreviated as CD) is a protocol used for the identification and investigation of cell surface molecules providing targets for immunophenotyping of cells.

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infection

## Hormones and Enzyme Deficiency and Immunodeficiency



Immunology

#### African Pygmies:

Normal Growth hormone level, lack of Somatomedin C

#### Pseudocholinesterase:

- Produced by the liver and circulating in plasma, deficient in liver failure
- Pseudocholinesterase deficiency can be caused by mutations in the BCHE gene
- The main complication resulting from Pseudocholinesterase deficiency is the possibility of respiratory failure secondary to Succinylcholine or mivacurium-induced neuromuscular paralysis.

#### Myeloperoxidase deficiency: MPO

- Myeloperoxidase (MPO) is a human enzyme in the azurophilic granules of neutrophil and in the lysosomes of monocytes
- If infectious disease occurs, it usually fungal infection, particularly Candida albicans that occurs in those who also has DM

#### Branched-chain ketoacid dehydrogenase deficiency—BCKD

Deficiency of this enzyme cause Maple syrup urine disease (MSUD)

#### Deficiency of arylsulfatase:

 Metachromatic leukodystrophy is the most common leukodystrophy caused by the deficiency of arylsulfatase. Myelin can't be degraded and accumulates in lysosomes.

#### Adenosine deaminase Deficiency:

- Adenosine deaminase (ADA) deficiency is an inherited disorder that damages the immune system and causes severe combined immunodeficiency (SCID).
- Adenosine deaminase deficiency is caused by mutations in the ADA gene.
- This condition is inherited in an autosomal recessive pattern
- The main symptoms of ADA deficiency are pneumonia, chronic diarrhea, and widespread skin rashes.
- Commonly present with Pneumocystis carinii pneumonia and failure to thrive
- Most individuals with ADA deficiency are diagnosed with SCID in the first 6 months of life. Without treatment, these babies usually do not survive past age 2.

#### W Glucose-6-phosphatase:

\* It is absent in muscle

#### Selective IgA deficiency:

- Most common primary Immunodeficiency
- Can present with sinopulmonary infection, GI infection, autoimmune disease
- Give false-positive beta-HCG test due to the presence of Hetrophile antibody
- Increase susceptibility to Giardiasis

## X-linked (Bruton's) Agammaglobulinemia:

- X-linked recessive, no B-cell maturation
- Recurrent bacterial infections after 6 months (decrease maternal IgG) as a result of

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#### Natural passive immunity Natural active immunity Babies get short-term protection from The Body makes own antibodies after the mother's antibodies via placenta or getting sick and recovering from an

#### Artificial passive immunity Artificial active immunity

breast milk

The Body makes own antibody after injection of dead or weakened pathogens----vaccination-like DPT vaccination etc.

Injection of antibodies (immunoglobulin) to fight some serious infection

### **HLA Subtypes Associated with diseases**

S/NO	HLA-subtype	Associated disease
1.	DR2	Multiple sclerosis, Good's pasture syndrome, Hay fever and SLE
2.	DR3	Grave's disease and Type 1 DM
3.	DR4	Rheumatoid arthritis and Type 1 DM
4.	DR5	Pernicious anemia and Hashimoto's thyroiditis
5.	DQ2/DQ8	Celiac disease
6.	A3	Hemochromatosis
7.	B8	Myasthenia Gravis, Graves' disease and Addison disease
8.	B5	Behcet disease

### Name of various disease Along with their Antibody

- ----idiopathic thrombocytopenic purpura (ITP) Anti-platelet antibodies---
- Anti-Neutrophil antibodies——vasculitis
- Anti IgM antibodies——— rheumatoid arthritis
- Anti-Histone antibodies-----drug-induced SLE
- Anti Gliadin antibodies-----celiac disease
- Anti-centromere antibodies-----scleroderma (crest)
- Anti-basement antibodies----- Good pasture's syndrome Heterophile antibodies -----infectious mononucleosis
- Anti-mitochondrial antibodies----------Primary Biliary cirrhosis
- Antibody against acetylcholine receptor----- Myasthenia gravis

NASEEM SHERZAD FCPS -1 HIGH-YIELD

Auto-antibody against calcium channel ----- Lambert eaten myasthenia syndrome

#### opsonization defect

- Decrease immunoglobulin of all types
- Skin graft will more successful in Agammaglobulinemia
- Live vaccine contraindicated
- Absent/scanty lymph nodes and tonsils

#### Common variable immunodeficiency:

- Defect in B-cell differentiation
- Usually presents after 2 months and maybe considerably delayed
- Increase the risk of autoimmune disease, bronchiectasis, lymphoma, sinopulmonary infection
- Decrease plasma cells and immunoglobulins

#### Thymic aplasia (DiGeorge syndrome)

- Failure to develop 3<sup>rd</sup> and 4<sup>th</sup> pharyngeal pouches
- Thymus and parathyroid gland fail to develop
- Absent thymic shadow on CXR
- Present with:
  - o Hypocalcemia-----Tetany
  - o T-cell deficiency-----Recurrent viral/fungal infection
  - o Congenital heart and great vessels defect

#### Chronic granulomatous disease:

- Lack of NADPH oxidase-----decrease reactive oxygen species—and absent respiratory burst in neutrophil
- Increase susceptibility to Catalase positive organism (staph aureus, E-coli, aspergillus)
- Abnormal Dihydrorhodamine (DHR) flow cytometric analysis

#### Job Syndrome:

- The Autosomal dominant <u>hyper-lgE syndrome</u> is also known as JOB syndrome, is a condition that affects several body systems particularly the immune system.
- Recurrent infections are common in people with this condition

#### P-ANCA Positive

- Churg struss syndrome
- Ulcerative colitis

#### **Onion Skinning**

- Primary sclerosing cholangitis
- Malignant hypertension

#### Psammoama Bodies ---- Mnemonic: PSaMMoma

- Papillary carcinoma of the thyroid
- Serous tumor of the ovary
- Meningioma

#### **Key Points**

- Ewing sarcoma
- Lyme arthritis

- Mesothelioma

# CHAPTER 23 MICROBIOLOGY

#### Pigments-producing Bacteria

Organism	-	Pigments
Staphylococcus aurous		Golden Yellow Pigment
Actinomyces Israeli	1	Yellow "Sulfur" granules, <u>Talcum granules</u> , prominent constituent of which is mass of filaments and pus (organism))
Pseudomonas aeruginosa	•	Blue-green pigment, Pyocyanine, Pyoverdin

#### Main features of Exotoxin and Endotoxin

Property	Exotoxin	Endotoxin
Secreted from cell	Yes	No
Clinical effects	Various effect	Fever and shock
Typical disease	DBT: Diphtheria, Botulism ,Tetanus	Meningococcemia
Mode of action	Various mode	Induce TNF and IL-1
Vaccine	Toxoid used as a vaccine	No toxoid, no vaccine
Toxicity	High:	Low

#### **Special Culture Requirements**

BUG	Media used for isolation		
C. Diphtheria	Tellurite plate, Loffler's media		
B. Pertussis	Bordet-Gengou (potato) agar		
M-Tuberculosis	Lowenstein-Jensen Agar		
H-Influenzae	Chocolate agar with factor 5 & 10		
M. pneumonia	Eaton's Agar		
	Sabouraud's agar		
N. Gonorrhea and N. Meningitides	Thayer-Martin (or VPN) media		
N Gonorrhea and N. Weillie			

Microbiology

#### INFECTIVE ENDOCARDITIS

- The most common overall cause of infective Endocarditis is streptococcal viridians.
- The most common cause of <u>acute infective Endocarditis</u> staphylococcus aureus which occurs on a previously normal heart valve.
- The most common cause of sub-acute infective Endocarditis streptococcus viridians, which occur on previously abnormal heart value
- The most common cause of infective Endocarditis in <u>IV drug users is staphylococcus aureus and</u> the most common valve involved in IV drug users is the Tricuspid valve.
- The most common organism which produces infective Endocarditis related with Prosthetic valves in long runs is staphylococcus epidermidis.
- The most frequently involved valve is the Mitral valve.
- Blood culture is the investigation of choice for Infective Endocarditis.

- The most common cause of community-acquired pneumonia is Streptococcus pneumonia (Rust color sputum).
- Most common cause of Nosocomial pneumonia is Pseudomonas aeruginosa. It is also the most common cause of ventilator associated pneumonia
- Pneumonia more common in young people is Mycoplasma pneumonia which is the most common atypical pneumonia and generally follows a more indolent course (walking pneumonia)
- Pneumonia worse on CXR but clinically asymptomatic or no cough etc. is Mycoplasma Pneumonia
- Hemolytic anemia is the occasional complication of mycoplasma pneumonia and for confirmation of hemolytic anemia, we use cold agglutination test, which is positive in hemolytic anemia.
- Pneumonia most common in elder is Haemophilus influenzae.
- Staphylococcus aureus: Normally causes pneumonia after a proceeding influenza virus infection and is the most common cause of pneumonia in IV drug abuser.
- Pneumonia associated with water coolers, air conditioning, immunocompromised and alcoholic is Legionella pneumonia, which is clinically detected by the presence of antigen in urine and lab show Hyponatremia.
- Klebsiella pneumonia causes lobar pneumonia in alcoholic and diabetic when aspirated. It produces "Current jelly" sputum which is Red brown in color and is composed of blood-tinged, thick and mucoid sputum. Klebsiella is cataalse positive and oxidase negative
- Pneumocysitis Jiroveci (boat-shaped organism) is the most common pathogen causing pneumonia in AIDS patients (AIDS defining disease).
- Sputum culture------diagnostic

#### **MENINGITIS**

- Overall: Streptococcus pneumonia is the most common cause
- Neonates: Group B streptococci (streptococcus agalactia)>E-coli>listeria monocytogenes (mnemonics BEL)
- Adult: H-influenza, Nesisseria meningitides &listeria monocytogenes
- Elderly: Streptococcus pneumonia and listeria monocytogenes
- In immunocompromised (HIV) patient, the most common cause is Cryptococcus neoformans (fungus).
- Meningitis after Pyogenic lung abscess is caused by Staphylococcus aureus
- CSF examination is the investigation of choice, other investigations include blood culture, CBC, chest X-ray, CT scan, EEG
- Nuchal rigidity is the Pathognomonic sign of meningeal irritation

#### Complication of meningitis

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- ✓ Cranial nerve palsies---- CN 3 (effected in tubercular meningitis) and CN 8 (effected in tubercular meningitis). Pyogenic meningitis)
- ✓ Recurrent seizure (epilepsy)

#### & CSF finding in Meningitis: very imp

- Protein level (normal= 20-40mg/dl): Elevated in all type of meningitis.
- Glucose (normal= 45-80mg/dl): low in bacterial and tubercular because bacteria consume glucose and normal in viral meningitis.
- WCC (normal 0-5 cells/uL): increase of PMN's (neutrophil) in bacterial (acute Pyogenic) and increase lymphocytes level in viral and tubercular meningitis.

#### High yield Points:

- Definition: inflammation of bone and bone marrow
- Spread can occur by local extension, direct implantation and hematogenous. The hematogenous is the most common route.
- Acute Osteomyelitis is usually beginning at Metaphysis.

#### Sequestrum:

✓ A macroscopic piece of dead bone is called Sequestrum.

#### Involucrum:

- ✓ New bone formed around an area of Osteomyelitis in response to periosteal stimulation is called Involucrum.
- Subacute Osteomyelitis: It is a distinct form of Osteomyelitis and brodie abscess is one type of subacute Osteomyelitis. the same beauty because special parties operate the

#### Microorganism

- The most common organism: Staphylococcus aureus (80-90%)
- Most common organism in Intravenous drug users: Staphylococcus aureus
- Most common organism in neonates: Haemophilus influenzae
- Most common organism in sickle cell disease patient: Salmonella
- No organism found in: 50%
- Diagnostic test is: Blood culture

Microbiology

## Urinary tract infection (UTI)

#### Organisms: (Mnemonic KEEPS)

- Klebsiella
- E-coli----most common overall cause of UTI
- Enterococcus
- Proteus and Staphylococcus

#### Investigation:

- Urine culture is a gold standard investigation
- UTI----Presence of a pure growth of > 10<sup>5</sup> organisms per mL of the fresh mid-stream urine sample
- Increased leukocyte esterase----- a marker of WBC
- Increase Nitrates----a marker of bacteria
- Sterile Pyuria-----presence of WBC's in urine with negative urine culture
- Sterile Pyuria is a feature of:
  - ✓ Renal tuberculosis-----most common
  - ✓ Treated UTI< 2 weeks prior
    </p>
  - ✓ Inadequately treated UTI
- Asymptomatic bacteriuria warrants treatment
  - ✓ Pregnant women
  - ✓ Infants
  - ✓ In those with urinary tract abnormalities

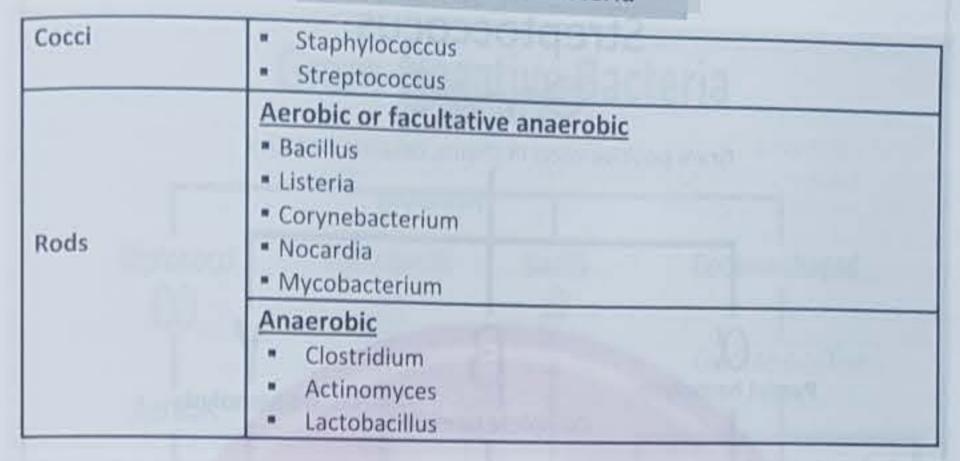
#### Treatment:

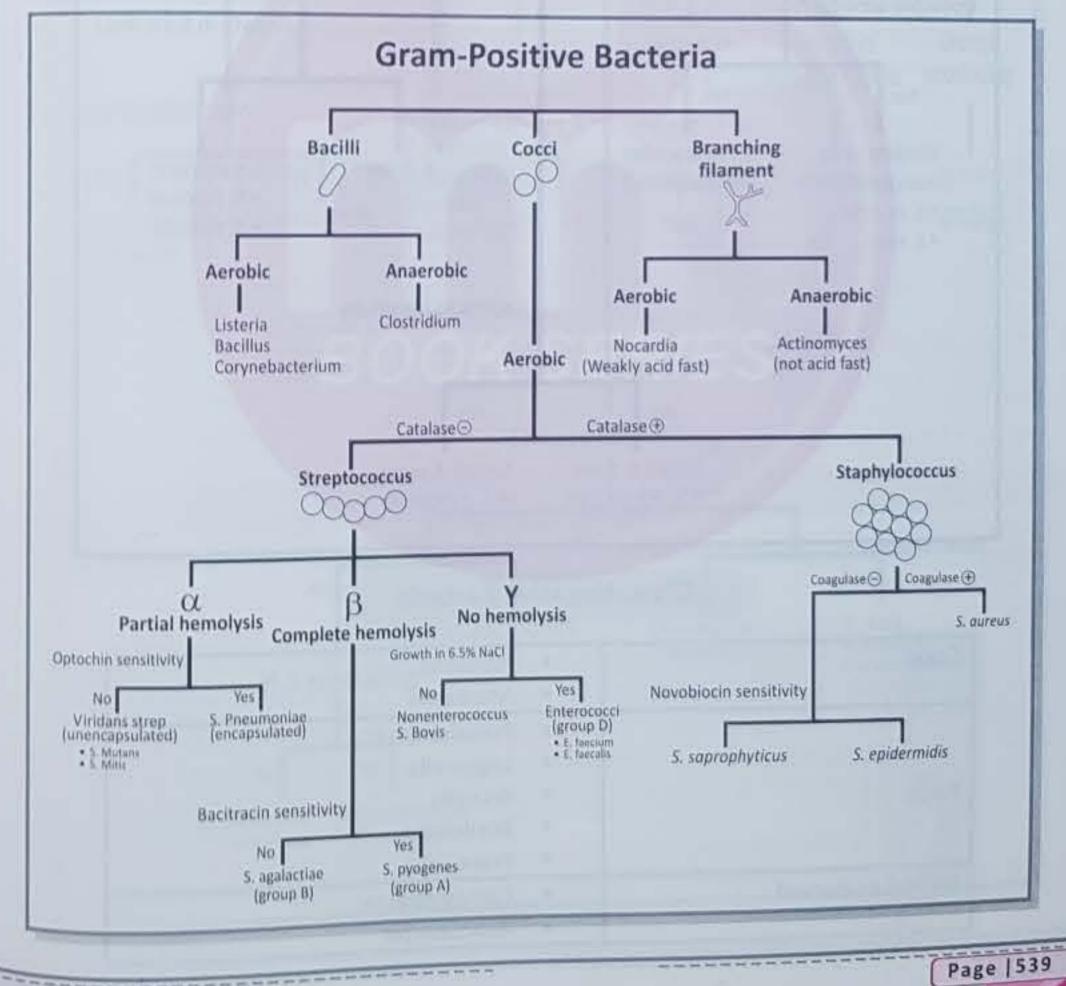
- General measure:
  - ✓ Fluid intake of at least 2 L per day.
  - √ Cranberry juice
  - ✓ Urinary alkalinizing agent such as potassium citrate
- Uncomplicated lower UTI
  - ✓ Trimethoprim-sulfamethoxazole is the best initial treatment
  - ✓ Second-line choices are: Amoxicillin, nitrofurantion

#### Liver Abscess

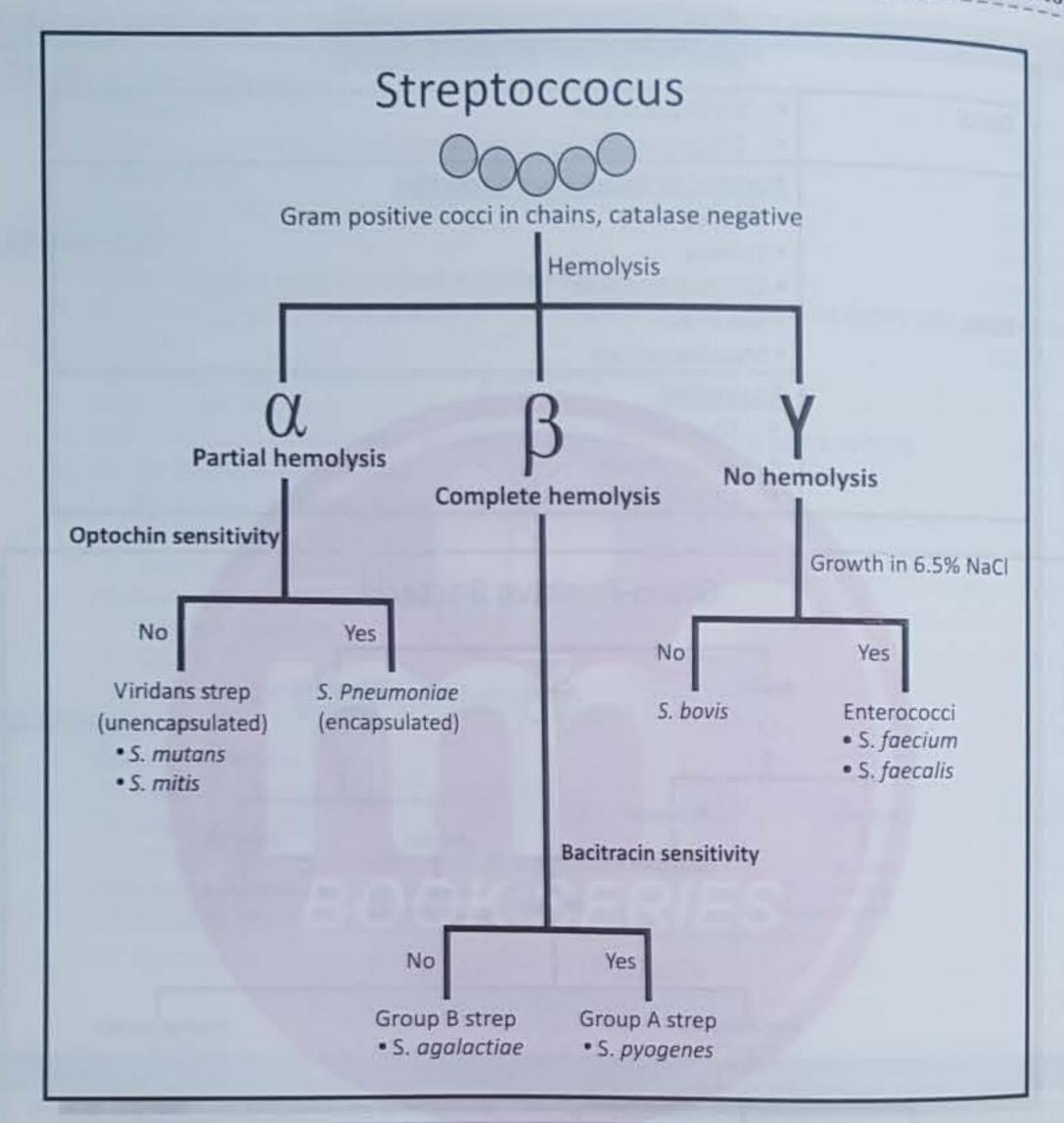
	Amoebic Liver Abscess	Pyogenic Liver Abscess
	It is the involvement of liver tissue by Trophozoites of the organism Entamoeba histolytica and of its abscess due to necrosis.  Jaundice is uncommon, jaundice is common presentation in Pyogenic liver absences Most commonly location in right lobe of liver	<ul> <li>The infection is caused by bacteria and is usually polymicrobial, with E. coli and K. pneumonia being the common causative organisms.</li> <li>Right lobe is affected twice as often as the left lobe</li> </ul>
*	Note: Rectal biopsy for amoebic abscess, we look forPSA	Diagnostic test:
	Initially treated with Metronidazole monotherapy	<ul> <li>Initially treated with Percutaneous catheter drainage and antibiotics</li> </ul>

**Gram-Positive Bacteria** 



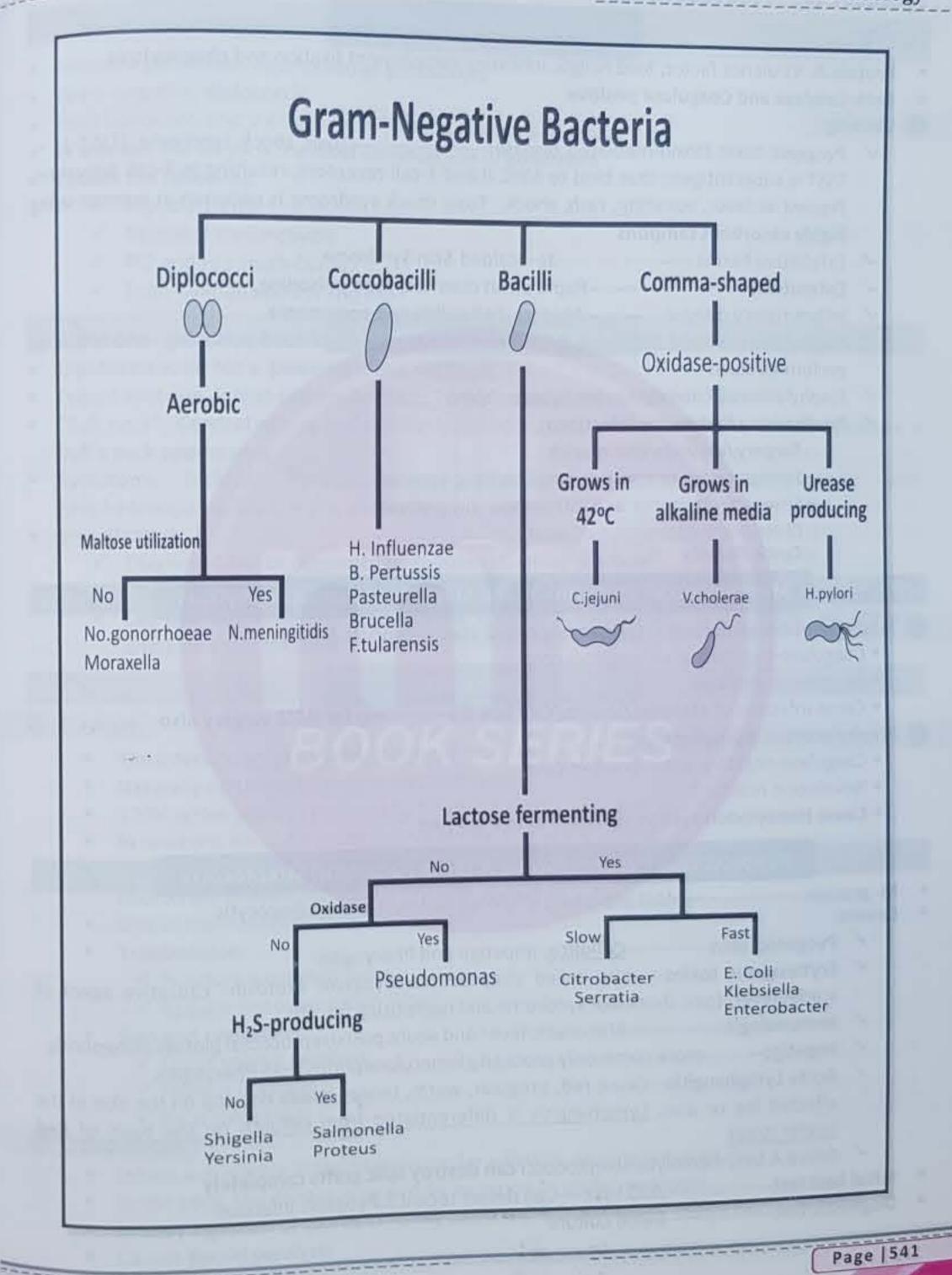


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#### **Gram-Negative Bacteria**

Cocci	<ul> <li>Neisseria</li> </ul>	
	<ul> <li>Moraxella</li> </ul>	
The second secon	<ul> <li>Pseudomonas</li> </ul>	
	<ul> <li>Legionella</li> </ul>	
Rods	* Brucella	
Rous	<ul> <li>Bordetella</li> </ul>	
	<ul> <li>Francisella</li> </ul>	
Helical or curved	<ul> <li>Campylobacter</li> </ul>	
	<ul> <li>Helicobacter</li> </ul>	



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NASEEM SHERZAD FCPS -1 HIGH-YIELD

## Staphylococcus Aureus

- Protein A: Virulence factor, bind Fc-lgG, inhibiting complement fixation and phagocytosis
- Both Catalase and Coagulase positive
- Causing:
  - ✓ Pyogenic toxin (toxin-mediated disease)-----Toxic shock syndrome (TSST-1) --TSST is superantigens that bind to MHC II and T-cell receptors, resulting in T-cell activation. Present as fever, vomiting, rash, shock. Toxic shock syndrome is common in women using highly absorbent tampons
  - Exfoliative toxins ------3s-Scalded Skin Syndrome
  - Enterotoxin-----Rapid onset diarrhea, food poisoning,
  - Inflammatory disease ------Abscess, Folliculitis and pneumonia
  - Staphylococcus food Poisoning is the most common form of food poisoning and is due to performed toxin
  - ✓ Staphylococcus Enterotoxin are superantigens
  - Predisposing factors for infections:
    - o Surgery/wounds/thorn prick
    - o Foreign body (tampon, surgical packing, sutures)
    - o Severe neutropenia and Intravenous drug abuse
    - o Chronic granulomatous disease
    - o Cystic fibrosis

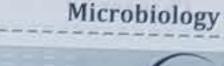
### Staphylococcus epidermidis and Staphylococcus Saprophyticus

- Staphylococcus epidermidis: (previously called staphylococcus Albus)
- · Coagulase-negative, gram-positive cocci
- Novobiocin sensitive
- Cause Infection of catheter/shunts/CVP line tip-----imp for IMM surgery also
- Staphylococcus saprophyticus:
  - · Coagulase-negative, gram-positive cocci
  - Novobiocin resistant
  - Cause Honeymoon cystitis /sexually active women

### Streptococcus Pyogens/Group A (Beta-hemolytic) Streptococci

- M- protein-----Most important virulence factor, it is anti-phagocytic
- causes:
  - ✓ Pyogenic toxin-----Cellulitis, impetigo and Pharyngitis
  - Erythrogenic toxins----also called streptococcal Pyogenic exotoxin---causative agent of scarlet fever, toxic shock like syndrome and necrotizing fasciitis
  - Immunologic-----Rheumatic fever and acute poststreptococcal glomerulonephritis
  - Impetigo----more commonly proceed glomerulonephritis than Pharyngitis
  - Acute Lymphangitis-cause red, irregular, warm, tender streak develop on the skin in the affected leg or arm. Lymphangitis is differentiated from cellulitis on the basis of Red tender streak
  - ✓ Group A beta-hemolytic streptococci can destroy split grafts completely
- ------ASO titer----Can detect recent S.Pyogenic infection Initial best test---
- Diagnostic test------Blood culture

## Neisseria Gonorrhea



- Neisseria gonorrhea, also known as gonococcus
- Gram-negative, diplococcic

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- Both Gonococci and meningococci, ferment glucose and produce IgA
- women, the cervix is the most common site of gonorrhea
- Causes the following:
  - ✓ Septic arthritis
  - ✓ Neonatal conjunctivitis
  - ✓ PID and Fitz-Hugh-Curtis
  - Tubo-ovarian abscess and PID

#### Corynebacterium Diphtheria

- Diphtheria toxin has a powerful effect on heart
- Potent exotoxin, inhibit protein synthesis via ADP-ribosylation of EF-2
- "Bull neck": Cervical edema and cervical lymphadenopathy from diphtheria infection produce a bull's neck appearance
- · Symptoms include: Pseudomembrane Pharyngitis (grayish-white membrane), with lymphadenopathy, Myocarditis and arrhythmia
- Investigation:
  - ✓ Diagnosed can be confirmed by culture in Loeffler medium.
  - Throat or skin swab should be sent for smear and culture
  - ✓ Lab diagnose based on gram-positive rods with Metachromatic (blue and red) granules and Elek's test for toxin

C. tetani:

### Clostridium

- The Infection spread VIA motor nerve
- Naturally occurring tetanus is descending type
- 100% active immunity offered by tetanus toxoid(inactivated toxin)
- In newborn the commonest source of infection is the umbilicus
- Block release of inhibitory mediators (Glycine and GABA) at spinal synapses, excitatory neuron are unopposed causing extreme muscle spasm
- One of the most toxic substance known
- Transmission:
  - ✓ Puncture wounds/trauma
  - ✓ Require low oxygenation tissue
- Sign and symptoms:
  - √ Cause spastic paralysis
  - ✓ Trismus (lockjaw)
  - ✓ Risus sardonicus

#### C. Botulinum:

- Inhibit Ach release at the neuromuscular junction, causing botulism.
- In the adult, the disease is caused by ingestion of preformed toxin
- In baby ingestion of spores in honey cause the disease called "floppy baby syndrome"
- Causes flaccid paralysis

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Microbiology

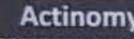
C. Botulinum causes botulism. Botulism is a severe, an often fatal form of food poisoning characterized by pronounced neurotoxic effects

#### C. Perfringens:

- Produce alpha-toxin, <u>"Lecithinase" a Phospholipase</u> that can cause myonecrosis (Gas Gangrenes) and hemolysis
- Cause myonecrosis or gas gangrenes a life-threatening disease
- Cause of death in gas gangrene is toxemia

#### C. Difficile:

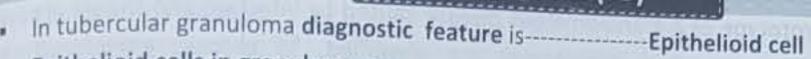
- Produce two toxins:
  - ✓ Toxin A, Enterotoxin, bind to brush border of the gut
  - ✓ Toxin B, cytotoxin, destroy the cytoskeletal structures of enterocytes causing Pseudomembrane colitis. Often secondary to antibiotic use, especially Clindamycin or Ampicillin. Treatment of Pseudomembrane colitis is, first line is oral Metronidazole, IV vancomycin is the second line.
- Diagnosed by detection of one or both toxin in stools



#### Actinomyces Israelii

- This organism is part of the natural flora of the mouth
- Actinomyces israelii is an anaerobic gram-positive bacterium that causes purulent abscesses and sinus tract formation
- This organism can affect the cervicofacial, pulmonary/thoracic, gastrointestinal, and female reproductive tract.
- Cervicofacial actinomycosis is the most frequent clinical form of actinomycosis, and "lumpy jaw syndrome", which is associated with odontogenic infection, is the most common clinical manifestation In cervicofacial Actinomycosis, Actinomyces israelii causes a granulomatous suppurative infection of the soft tissues in and around the mandible.
- Patients present with a hard swelling associated with the jaw (lumpy jaw). As the swelling progresses, a bluish discoloration of the skin appears. Over time, a fistulous abscess forms within the hard swelling and sinus tracts develop. A yellowish purulent material is usually discharged from these sinuses.
- Genitourinary tract Actinomycosis is the second most frequent clinical form of actinomycosis. The main clinical feature of genitourinary tract actinomycosis is pelvic actinomycosis in women using an intrauterine device (IUD)
- \* Respiratory tract actinomycosis includes pulmonary, bronchial, and laryngeal actinomycosis. Pulmonary actinomycosis is the third most common type of actinomycosis, after that occurring in cervicofacial and abdominopelvic locations
- Actinomyces causes solitary brain abscess, while Nocardia will produce multiple foci
- . The IUCD-associated incidence of Actinomyces israelii in the female genital tract is common
- Diagnosis:
  - ✓ Identifying gram-positive branching Bacilli in "sulfur granules"
  - ✓ Colonies resemble molar teeth

Tuberculosis (TB)



- Epithelioid cells in granuloma are------Macrophages
- . When epithelioid cell fuse together form-------Multinucleated giant cell
- There is no cavitation in------Primary Tb
- Langerhans cells are characteristic of-----Secondary TB
- Positive Mantoux test:------Prior infection with TB
- TB antibody are -----Cell bounded
- TB remains active in sputum for-----20 hour
- BCG confers------Active immunity
- Most common finding in genitourinary TB is------Sterile Pyuria
- This is the most common organism associated with hypersensitivity reaction
- · Not present in the female urinary tract
- Slowest growing human bacterial pathogens
- Most common complication of pulmonary TB is bronchiectasis
- The Protective value of BCG vaccination is less than 40%
- Tuberculin/Mantoux test is negative in those who are taking immunosuppressant

#### Investigation

- The Initial test for TB: -----Chest X-Ray
- Definitive Diagnosis of TB-----Sputum AFB
- Microscopic/histopathology finding that suggests TB-----Caseous necrosis

#### Tuberculosis (Some Terminology in simple way)

- Once inhaled the organism bacilli and lodge in the alveoli bacilli then initiate the recruitment of macrophage and lymphocyte.
- Tubercular granuloma:
  - Macrophage undergo transformation into epithelioid and langhans cells which aggregate with the lymphocyte to form the classical tubercular granuloma.
- Ghon focus:
  - It is the primary lesion characterized by aggregation of numerous granulomas in the periphery of the lung.
- @ Gohn complex:
  - It refers to combination of calcified primary lesion (i.e. Ghon focus) with lymphoid involvement. This is the only characteristic of primary tuberculosis.
- Miliary TB:
  - \* It refers to acute diffuse dissemination of tubercular bacilli via bloodstream (homogenous)
  - Chest X-ray show "Millet-seed" appearance

#### Granulomatous inflammation

- Tuberculosis is the prototype of a granulomatous disease caused by infection and should always be excluded as the cause when granulomas are identified. In chronic granulomatous inflammation, the most predominate process is the proliferation
- Rounded or stellate granuloma/suppurative granuloma containing central granular debris and recognizable neutrophils; giant cells uncommon------Cat-scratch disease (Bartonella Henselae)
- Leprosy (loss of sensation, anesthesia), initial investigation------Nasal scraping
- Coin lesion on X-ray ------Granuloma

#### Naseem Sherzad High-Yield Points

- Non-caseating granuloma with sputum AFB positive----leprosy
- Non-caseating granuloma with <u>AFB negative</u>————Sarcoidosis
- Non-caseating granuloma in up to 50% patients-----Crohn disease
- Gummas observed in------Tertiary stage of syphilis
- Abscess and granuloma------Actinomyces Israeli
- Nasal deformity + granuloma + acid-fast bacilli------Leprosy
- Nasal deformity+ granuloma + Hematuria and c-ANCA positive---- Wagner disease

#### Pseudomonas

- Oxidase (usually) and Catalase positive.
- Classified as an opportunistic pathogen
- Liver is the primary target
- DOC of choice----Aminoglycosides-----Ciprofloxacin
- Cause greenish pus discharge
- Most strains of P. AERUGINOSA produce one or more pigments, including pyocyanin (bluegreen), pyoverdine (yellow-green and fluorescent), and pyorubin (red-brown).
- It gives pale colonies on Mackoneky medium because it is non-lactose fermenter

#### Rickettsia

- They are obligate intracellular parasite
- Cell divide by binary fission
- Multiply in the endothelial cells of small blood vessels
- Rickettsia cause
  - ✓ Rocky mountain spotted fever
  - ✓ Q.fever
  - ✓ Epidemic typhus
  - Endemic typhus and Scrub typhus
- Weil flex reaction, complement fixation test and Immunofluorescence assay are the serological test for Rickettsia, animal inoculation test can also be done
- In Rickettsia, enzymes for the biosynthesis of this co-factor appear to be limited

Salmonella Typhi



Microbiology

. Found only in human

Chapter 23

- Rose spot present on 7th 10th days
- Primarily involving the lymphoid tissue (Payer patches)
- Can remain in the gallbladder and cause a carrier stat

#### Investigation: BASU

- Fist week-----Blood culture
- 2<sup>nd</sup> week------Antibody/Widal test (1:160 of H and O antigen)
- 3rd week-----Stool
- 4<sup>th</sup> week------Urine culture

#### Syphilis 🗼

- \* Syphilis is a sexually transmitted disease (STD) caused by an infection with bacteria known as Treponema Pallidum
- For initial diagnosis, sample can be taken from Genital sore scrapping
- 1) Primary:
  - ✓ Localized disease with a painless chancre
- 2) Secondary:
  - ✓ Condyloma latum
  - ✓ Maculopapular rash
- 3) Tertiary:
  - ✓ Gummas (chronic granuloma)
  - √ Tabs dorsalis
  - ✓ Argyll Robertson pupil
  - ✓ Broad base ataxia, positive Romberg, Charcot joint
  - ✓ Stroke without hypertension
- 4) Congenital:
  - ✓ Saber shins , saddle nose, CN 8 deafness
  - ✓ Hutchinson's teeth, mulberry molars
  - ✓ Early presentation is key, as Placental transmission occurs after 1st trimester.
  - ✓ Congenital syphilis can be best diagnosed by IgM FTAbs

#### Vibrio Cholera

- Comma shaped organism
- Transmitted by food and water
- \* Cholera is an infectious disease that causes severe watery diarrhea/fatal diarrhea, which can lead to dehydration and even death if untreated. Also remember that most serious food poisoning which can lead to death is caused by clostridium Botulinum
- A person with cholera can quickly lose fluids, up to 20 liters a day, so severe dehydration and shock can occur.
- They are oxidase-positive
- Sensitive to stomach acid and Grow in alkaline medium>>resistant to Alkaline medium
- Produce profuse rice-water diarrhea via toxin that permanently activates Gs, increase cAMP
- V-cholera can ferment sucrose and Mannose but not arabinose
- A positive oxidase test result is a key step in the identification of V- cholera and other vibrios

### Chapter 23

Microbiology

## Virology

**Basic Concept** 

## DNA virus----all replicate in the nucleus except Poxvirus

- RNA virus----all replicate in cytoplasm except influenza virus and retroviruses ]
- Virus ploidy---all virus are haploid (with 1 copy of DNA or RNA) except retrovirus, which have 2 identical ssRNA molecule = diploid
- Naked virus (non-enveloped) include------Papilloma virus, adenovirus, picornavirus, polyomavirus, calcivirus, parvovirus, Reovirus, Hepevirus

#### DNA virus:

- ✓ Are HHAPPPPy viruses------Hepadna virus (HBV), Herpes, Adeno, Pox, Parvo, Papilloma, Polyoma
- ✓ Are double strand-----except Parvo (single strand)
- ✓ All are linear——except Papilloma, polyoma and Hepadna (circular)

#### RNA virus: ✓ Viruses:

- o Flavivirus------Dengue, yellow fever, HCV, west Nile virus
- Picornavirus-----Polio, HAV, coxsackievirus (aseptic meningitis, herpangina, hand, foot and mouth disease, Myocarditis ), rhinovirus(common cold), echovirus--aseptic meningitis
- Paramyxoviruses-----Parainfluenza---Croup, Mumps, Measles
- Retrovirus: have reverse transcriptase, HTLV----T-cell leukemia, HIV----AIDS
- o Hepevirus-----HEV
- o Togavirus (rubella), Coronavirus , Calicivirus,
- ✓ All are ssRNA (like our mRNA) except Reoviridae virus (human rota virus) which is dsRNA---remember Reo biscuit is double coated

### Epstein Barr Virus (EBV)

Epstein-Barr virus (EBV), also known as human herpes virus 4, is a member of the herpes virus family. It is one of the most common human viruses. EBV is found all over the world. Some facts and associated malignancy of EBV:

- For Oropharyngeal carcinoma remember-----HPV is the risk factor
- Burkitt lymphoma-----EBV (strong association is due to African genome)
- Non-Hodgkin lymphoma-----EBV
- Hairy tongue-----EBV
- Lymphoma in AIDS-----EBV Infectious mononucleosis----EBV
- Burkitt lymphoma oncogenesis by EBV------Protoncogens C-Myc amplification
- N-Myc gene amplification occurs in------Neuroblastoma
- No vaccine available against-----EBV
- EBV is Hetrophile positive and CMV is Hetrophile negative

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## Microbiology

### Leptospirosis—Weil's disease Leptospirosis is a zoonosis with a worldwide distribution.

- The etiologic agent of Leptospirosis is motile spirochetes
- Water is an important vehicle in its transmission.
- Epidemics of Leptospirosis may result from exposure to flood waters contaminated by urine from infected animals
- Source of infection———Rat urine and Mice
- It is associated with 3 Rs----Rats, Ricefields and rain-fall
- Warthin-Starry stain (WS)----- considered the best stain for detection of Spirochetes

#### Brucella Brucellosis is transmitted by———— -----unpasteurized milk

- · Facilitated intracellular pathogens
- · Potential warfare agent
- Serological confirmation of disease is most common

#### Important species:

- ✓ Brucella abortus-----Cattle
- ✓ Brucella melitensis

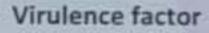
  ——Goat

#### Acute Brucellosis classic triad:

- Undulant high fevers
- Drenching sweats
- Migratory arthralgias and myalgias



#### E-coli



- ✓ Fimbriae------Cystitis, pyelonephritis
- ✓ K-capsule———Pneumonia, neonatal meningitis
- ✓ LPS endotoxin-----Septic shock

### Most common in:

- Post-op infection and Abdominal surgery
- Most common cause of peritonitis/spontaneous bacterial peritonitis, the most common cause of Pyogenic peritonitis is Bacteroides
- Cause Traveler diarrhea
- Ascitic tap

#### Anthrax

\* Etiological agent: Bacillus anthracis, a large aerobic, spore-forming, gram-positive rod-shaped microorganism that is encapsulated (poly-D-glutamic acid) and non-motile

- Cutaneous (skin) anthrax: this form account for over 95% of anthrax cases
- Inhalational (pulmonary) anthrax: also known as woolsorter's disease
- \* Mood of transmission: direct transmission(through cutaneous contact with infected animals of contaminated animal products), indirect transmission(through ingestion of contaminated meal) and air-borne transmission (though inhalation of air contaminated by spores)
- \* Treatment: ciprofloxacin or doxycycline should be given for at least 60 days

### Infectious Mononucleosis

- Also known as Hetrophile-positive infectious mononucleosis
- Caused by EBV & characterized by fever, sore throat, lymphadenopathy & atypical lymphocytosis,
- Most of the causes are self-limited
- The infected cell in infectious mononucleosis are B-cell
- The Atypical cell that produces in response are T-cells (CD8+). CD8 cytotoxic T cells control proliferating B lymphocytes infected with EBV.
- CD8+ T- cells increase in numbers in the blood stream and are activated (also known as Downey cells, reactive lymphocytes or atypical lymphocytes because of their atypical presence in peripheral blood) to eliminate EBV infected B- lymphocytes.
- Having Longest incubation period and It is DNA virus
- Heterophile antibody (Monospot) is the diagnostic test, Downey cells may be present
- Splenic rupture is common among males than among females

#### Herpes Simplex Virus (HSV)

- Infected cell have intracellular cowdry A inclusion
- PCR is the test of choice
- Not a risk factor for malignancy
- Transmitted by droplet
- Treatment of pregnant and non-pregnant----acyclovir first choice
- Trifluridine can be given in non-pregnant, but acyclovir should always be on top

HSV-1	HSV-2
<ul> <li>✓ Cause gingivostomatitis</li> <li>✓ Latent in the trigeminal nerve</li> <li>✓ Spread by respiratory secretion, saliva secretion—droplet</li> </ul>	<ul> <li>✓ Herpes genitals and neonatal herpes</li> <li>✓ Latent in sacral ganglia</li> <li>✓ Sexual contact and perinatal</li> </ul>

### Vaginal infection (Tricky points)

- Condyloma acuminatum:
  - ✓ Condyloma acuminatum or Genital wart is a papilloma caused by -----HPV
  - ✓ Condylomata acuminata are exophytic cauliflower-like lesions that are usually found near moist surfaces. They may be observed in the perianal area, vaginal introitus, vagina, labia, and vulva. Genital warts may also be found on dry surfaces, such as the shaft of the penis.
- Condyloma lata, the flat papule of ----secondary syphilis---painless ulcer
- Chancroid is an STD caused by Haemophilus ducreyi. It is characterized by painful ulcer
- Vulvar itching and pinkish purulent discharge-----Trichomonas vaginalis
- Foul-smelling vaginal discharge with clue cell-----bacterial vaginosis
- Curable STDs that are usually non-ulcerative include gonorrhea, Chlamydia and trichomoniasis.
- Vaginitis most commonly caused by Candida, second most commonly caused by vaginalis

#### Microbiology

## Cytomegalovirus (CMV)

- Latent in mononuclear cell and is the Most common infection in transplant patient
- The Most common and most lethal organism in blood transfusion
- Infect cell has characteristic "owl eye inclusion"

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- CMV cause hypertrophy of cell due to increase iron uptake causing increase in cell growth
- Common cause of Chorioretinitis in AIDS patient
- This the Viral cause of Bronchogenic carcinoma

- Hall-marks of AIDS------Progressive immune deficiency
- Hall-mark of HIV------Proliferation of virus in T-cell and decrease cell-mediated immunity.
- Brain abscess------Toxoplasmosis
- Chorioretinitis-----CMV
- Otitis media ------Streptococcus pneumonia
- AIDS is not transmitted via saliva
- Post-HIV operation, the floor will be cleaned by 1% hypochlorite and instrument will be cleaned by 2% gluteraldehyde

#### Malignancy:

- ✓ Lymphoid tumor in AIDS-----EBV
- ✓ Most common skin cancer-----Kaposi sarcoma (the hard plate is the most common site and is due to HHVV-8
- ✓ Decrease CD4 count specifically TH-1 cell
- ✓ Patient of AIDS may have Cervical Carcinoma. Cancer rare in AIDS is leukemia

#### Phases/Stage of HIV:

- Stage 1: The primary HIV infection phase (or acute sero-conversion illness)
- Stage 2: The asymptomatic latent phase. The minor symptomatic phase
- Stage 3: The major symptomatic phase and opportunistic diseases
- Stage 4: AIDS-defining conditions: the severe symptomatic phase

#### Investigation

- Best initial test----- ELISA test
- Confirmatory test----Western test
- Infected infant------Diagnosed by PCR-RNA or viral culture
- PCR-RNA viral load test is used to measure the response to therapy (decreasing level is good), detect treatment failure and diagnosis HIV in infants
- Test useful for detection of HIV antigen during window period---P24 antigen capture assay

#### Rubella (German Measles)

- Rubella is caused by an RNA virus of the togavirus family
- Can be prevented by anti-rubella vaccine
- Active immunization against rubella is now possible with live attenuated vaccine
- Immunity: Rash in association with detection of IgM indicates recent infection. <u>IgG antibodies</u>
   persist for life

The classic triads of the congenital defect are

- · Cataract.....This is the most common one
- Deafness
- Cardiac malformation

#### Parvovirus B19

- Parvovirus B19 is a virus that causes a common childhood illness, also called "5<sup>th</sup> disease" or "erythema infectiosum."
- Single-stranded DNA virus, having no envelope and only known human parvovirus
- Pathogencity:
  - Fifth disease:
    - ✓ Erythema infectiosum
      - o "Slap cheek" rash on the face
      - o Lacy rash on the extremities
  - Aplastic crises in sickle cell disease:
    - ✓ Patients with hemoglobinopathies
    - ✓ Immunocompromised
  - Congenital Parvovirus:
    - ✓ Hydrops fetalis
    - ✓ Pregnant women exposed to B19 should have IgG and IgM serology

#### Measles

- . Measles (rubeola) is a highly contagious virus that can lead to complications.
- Subacute sclerosing panencephalitis (SSPE):
  - It is a Progressive neurological disorder of childhood and early adolescence.
  - It is caused by persistent defective measles virus
    - Most common cause of death in measles is: Pneumonia
    - Commonest complication of measles is: Acute Otitis media
    - Symptoms that last longest in measles is: Cough (10 days)
    - Pathognomonic sign in measles is: Koplik Spot
    - Prodromal phase: four Cs, cough, conjunctivitis, coryza & Koplik spot.

Hepatitis

Microbiology

## Hepatitis B:

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- ✓ Hepatitis B virus contains protoncogens
  - ✓ It is the most common cause of hepatocellular carcinoma.
  - ✓ It is the Most common hepatitis associated with Blood transfusion, but most dangerous/lethal is CMV
  - ✓ It is associated with Polyarteritis nodusa (PAN), membranous nephropathy and Membranoproliferative glomerulonephritis
  - ✓ Hepatitis B virus having prolong incubation period
- ✓ Hepatitis B is monitored by surface antigen

#### Mepatitis C:

- ✓ It is the most common cause of liver Cirrhosis
- ✓ It is the Most common cause of Chronic hepatitis--- C... C for chronic
- ✓ It is important to note that always prefer hepatitis C for Chronicity and hepatitis B for hepatocellular carcinoma the reason is that hepatitis C cause hepatocellular carcinoma through cirrhosis while hepatitis B can cause through cirrhosis and can directly without being through cirrhosis

#### # Hepatitis E:

- ✓ It is the Most common cause of mortality and most lethal hepatitis in pregnancy
- √ Hepatitis E causes Epidemics---E...E for epidemics

#### Naseem Sherzad High-Yield Points

- Most common cause of hepatitis in male/female (whether pregnant or non-pregnant)--hepatitis A
- Most common cause of fulminant hepatitis---hepatitis D
- Most common complication of fulminant hepatitis is cerebral edema
- Most common cause of liver cirrhosis in Asian population is alcohol, most common cirrhosis in Pakistan is viral hepatitis > alcohol
- Most common hepatitis in our population is Hepatitis-A
- Most dangerous/lethal infection in transfusion is CMV

#### Kissing

- Kissing bug------Reduviid bug --- A painless bite (much like a kiss)
- Kissing disease-----Infectious mononucleosis

## PARASITOLOGY

## Malaria

- Species causing benign tertian malaria————P-vivax
- Species causing malignant tertian malaria————P-falciform
- Spread to human in————————Sporozoites
- Inactive or dormant stage———Hypnozoites
- Sporozoite which divides inside hepatocyte is------Merozoites
- Malaria is associated with-----
  Hemolytic anemia
- Parasite rate-----5-15 years
- Type of anemia in malaria
   Normochromic Normocytic anemia
- Pyrimethamine: slow but long-acting erythrocytic schizonticide——MOA: inhibitor of plasmodial dihydrofolate reductase
- The most sensitive indicator of <u>Recent Malarial Transmission</u> In a Locality is ——Infant parasite rate
- The gametocyte of P. falciparum have a crescent or banana shape

#### Aspergillosis

- A fungal infection
- The majority of cases occur in people with underlying illnesses such as tuberculosis or chronic obstructive pulmonary disease (COPD), but with otherwise healthy immune systems
- Aflatoxin, produce most commonly by A. flavus and A. parasiticus, which is considered a human carcinogen. Alpha toxin is a toxin produced by the bacterium Clostridium Perfringens (C. Perfringens)... so don't mix both
- Cause Rhinosinusitis and medial necrosis and granuloma
- A fungus <u>ball in the lungs</u> may cause no symptoms and may be discovered only with a chest X-ray,
  or it may cause repeated coughing up of blood, chest pain, and occasionally severe, even fatal,
  bleeding.
- On chest X-ray and CT, pulmonary aspergillosis classically manifests as a halo sign, and, later, an air crescent sign
- The current medical treatments for aggressive invasive aspergillosis include voriconazole and liposomal amphotericin B in combination with surgical debridement

## Bugs hints (if all else fails)

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Organism	Characteristic		
Stap aureus	Pus, Empyema, abscess, catheter tip infection, Folliculitis, Surgical wound		
H-influenza	Pediatric infection (including Epiglottitis )		
Pseudomonas aeruginosa	Pneumonia in cystic fibrosis, burn infection, ventilator in ICU		
Clostridium Perfringens	Traumatic open wound		
Pasteurella multocida	Dog or cat bite		
HBV (from needle stick)	Health care provider		
Mucor or rhizopus ssp.	Fungal infection in diabetic or immunocompromised		
Candida albicans (systemic), aspergillus	Neutropenic patients		
Lyme disease	<ul> <li>Caused by spirochetes Borrelia Burgdorferi</li> <li>Transmitted by vector Ixodes scapularis tick</li> </ul>		
Streptococcus Agalactia (group B streptococci)	<ul> <li>Produce CAMP factors,</li> <li>Hippurate test positive, patient with positive culture receive intrapartum penicillin prophylaxis, colonize vagina</li> <li>Cause meningitis, pneumonia and sepsis, mainly in Baby</li> </ul>		
Bartholin cyst	<ul> <li>It results from obstruction of the Bartholin duct and is a soft painless mass.</li> <li>Most commonly infected by gonorrhea less by staph. Aureus</li> <li>The infected cyst is called Bartholin abscess which is painful</li> </ul>		
Chlamydia	<ul> <li>Most common cause of PID,</li> <li>Most common cause of STD,</li> <li>Cause lymphogranuloma venereum</li> </ul>		
Hydatid disease	<ul> <li>Also known as "Dog tape worm"</li> <li>Caused by the larval form of the Cestode worms, Echinococcus Granulosa and Echinococcus multilocularis</li> <li>Definitive host: dogs</li> <li>Intermediate host: cattle, sheep, human</li> <li>It can affect any organ, but liver is the most common followed by the lung</li> <li>70% are located in the right lob and are solitary</li> </ul>		

## Mosquito-borne Disease

Parasitic: Malaria, lymphatic Filariasis

Viral: Dengue fever, yellow fever, dengue hemorrhagic fever, Japanese encephalitis, Chikungunya

Bug	Hint for diagnosis
Taenia solium ova (cysticercosis)	✓ Brain cyst, seizure, caused by ingestion of egg of taenia solium
<ul> <li>Echinococcus granulosus (also called hydatid worm)</li> </ul>	✓ Liver cyst (hydatid cyst) ✓ Daughter cyst
Diphyllobothrium latum	✓ Vitamin-B12 deficiency
<ul> <li>Hook worm (Ankylostoma dudenali/nectar)</li> </ul>	✓ Microcytic anemia
<ul> <li>Schistosoma mansoni</li> </ul>	✓ Portal hypertension
Clonorchis sinensis	<ul><li>✓ Biliary tract disease</li><li>✓ Cholangiocarcinoma</li></ul>
Trichuris Trichiura (whipworm)	✓ Bloody diarrhea, Rectal prolapase, finger clubbing, vitamin A deficiency, may lead to iron deficiency anemia, has a narrow anterior esophageal end and shorter and thicker posterior end
* Ascariasis	✓ Intestinal and pulmonary symptoms, can cause acute appendicitis and pancreatitis by worms migration
Leishmania donovani	<ul> <li>✓ Visceral Leishmaniasis(Kala-Azar)</li> <li>✓ Unicellular flagellate intracellular protozoa</li> <li>✓ Pancytopenia, splenomegaly, hepatitis and spiking fever,</li> <li>✓ Sandfly</li> </ul>
Trypanosoma Cruzi	✓ C's, Chagas disease, Cardiomyopathy, megaColon, Reduvid bug
Onchocerca volvulus	✓ Hyperpigmented skin, river blindness
Paragonimus westermani	✓ Hemoptysis
Schistosoma Hematobium	✓ Bladder cancer, Hematuria
<ul> <li>Amoebiasis</li> </ul>	✓ It is a Protozoal infection cause by Entamoeba histolytica ✓ Trophozoites in the colon form "flask-shaped" ulcer in the sub-mucosa ✓ Amoeboma: it most commonly affects the CAECUM

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i	Naseem Sherzad	High-Viold Dains	

- Histoplasmosis primarily affect -------Reticuloendothelial system
- After lung abscess cause of pneumonia is------Staph aureus
- Generally, the cause of PID is ----- Chlamydia > gonorrhea
- Post abdominal gynecological infection------------------Bacteroides
- Puerperal sepsis------Group B streptococci
- . Human bites: injury to the ear, tip of nose and lower lip are most usually seen in victims of human bites. Anaerobic and aerobic organism prophylaxis is required as bite wounds typically have high virulent bacterial count.
- The finding that first suggested a biological difference in women susceptible to UTI is increased adherence of bacteria to vaginal cells
- . Candida infection is the most common infection of the vagina during 2nd and third trimester of pregnancy
- Shigella dysentery effect is due to----mucosal invasion
- \* A yellow fever cases occurring in non endemic area is called-----epidemic
- Sepsis------Blood culture is positive
- . The most common complication of cyst is an infection
- - A pilus is a hair-like appendage found on the surface of many bacteria and archaea.
  - Bacteria adhere to the cell by Pilli
- The virulence factor that is important for adherence is Pilli
- Ø Droplet transmission:
  - ✓ Droplet transmission occurs when bacteria or viruses travel on relatively large respiratory droplet that people sneeze, cough, drip or exhale
  - √ They travel-short distance before setting, usually less than 3 feet (1-2 feet) or 30-60 cm or 1 meter.
  - ✓ These droplets are loaded with infectious particles.
  - ✓ E.g. meningococcal meningitis, pertussis, mumps, rubella
  - ✓ Reference: K-Park , Page 93, 22<sup>nd</sup> edition
- Air born transmission:
  - ✓ If pathogen travel more than 1 meter (> 3 feet) it considered air born infection (3-6 feet) e.g. anthrax, chicken-pox, measles, small-pox, Tb
- \* Shwartzman phenomenon, also known as Shwartzman reaction, is a rare reaction of a body to particular types of toxins, called endotoxin, which cause thrombosis in the affected tissue
- \* Transformation: Ability to take up naked DNA (i.e. from cell lysis) from the environmental (also known as "competence"). A feature of many bacteria, especially S.penumonia, H. influenza type B and Neisseria. Any DNA can be used. Adding deoxyribonuclease to environment will degrade naked DNA in medium----no transformation seen
- \* Transposition: Segment of DNA that can "jump" (excision and reintegration) from one location to another, can transfer a gene from plasmid chromosome and vice versa. When excision occurs, It may include some flanking chromosomal DNA, which can be incorporated into a plasmid and transferred to another bacterium.

### Transduction:

- ✓ Generalized: A "packing" event. Lytic phage infects bacterium. Leading to cleavage of bacterial DNA. Parts of bacterial chromosomal DNA may become packed in viral capsid. Phage infect another bacterium, transferring these genes
- ✓ Specialized: An "excision" event. Lysogenic phage infects bacterium; viral DNA incorporated into the bacterial chromosome. When phage DNA excised, flanking bacterial genes may be excised with it. DNA is packaged into phage viral capsid and can infect another bacterium
- ✓ Virus transfer information from cell to another cell by Transduction

### Lysogeny, specialized transduction: ABCDE

Gene for the following 5 bacterial toxins encoded in a lysogenic phase

- ✓ ShigaA-like toxin
- Botulinum toxin
- Cholera toxin
- Diphtheria toxin
- Erythrogenic toxin of Streptococcus pyogenes

### Sterilization method of choice for article during surgery

- Linen (Gown, caps, mask, drapes)-----autoclaving
- Metal instrument——autoclaving
- Plastic instruments/components----ethylene oxide sterilization, formalin chamber
- Sharp edges instrument———ETO/hot air oven/chemical disinfection
- Alcohol-based hand hygiene product contains chlorhexidine gluconate, used for disinfection of hand
- Spore killed by dry heat at 160 °C for 1 hour or in autoclave heating at 121 °C for 15mins
- All samples for routine histology are immediately placed in fixative, usually formaling (10% formaldehyde) to preserver morphology and to prevent autolysis

### Systemic Inflammatory Response Syndrome (SIRS)

### Criteria: 2 or more of the following

- 1. Body temperature less than 36 °C or greater than 38 °C
- 2. Heart rate greater than 90 beats per minute
- 3. Tachypnea (high respiratory rate), with greater than 20 breaths per minute; or, an arterial partial pressure of carbon dioxide less than 4.3 kPa (32 mmHg)
- 4. White blood cell count less than 4000 cells/mm3 (4 x 109 cells/L) or greater than 12,000 cells/mm3 (12 x 109 cells/L)

#### Sepsis

SIRS + documented infection (Confirmed by culture etc)

### Sever sepsis

Sepsis + organ dysfunction or hypoperfusion (lactic acidosis Oliguria or altered mental status)

### Septic shock

Sepsis + organ dysfunction + hypotension (systolic BP <90mm Hg or >90 with vasopressin)

# C H A P T E R**EMBRYOLOGY**

### **Female Gametogenesis**

### Primordial germ cell:

- ✓ Gametes are derived from primordial germ cell that are formed in the epiblast during the 2<sup>nd</sup> week and that move to the wall of the yolk sac
- ✓ Arrive from the wall of yolk in the ovary on 6 weeks of development and differentiate into Oogonia

### Oogonia:

✓ Oogonia enter meiosis I and undergo DNA replication to form primary oocytes.

### Primary oocytes:

- ✓ All primary oocytes are formed by the fifth month of fetal life and remain dormant in prophase (dictyotene stage) of meiosis I until puberty
- ✓ Ovulation: During ovulation, a primary oocytes complete meiosis-I and secondary oocytes and a first polar body, which probably degenerates
- ✓ So ovulation gives us: Secondary oocytes and first polar body
- ✓ The Viscosity of Cervical mucosa is at peak on day 2 of ovulation.

### Secondary oocytes :

- ✓ Secondary oocytes enter meiosis II
- ✓ The secondary oocytes remain arrest in metaphase of meiosis II until fertilization occur

### Mature oocytes:

- ✓ Fertilization: at fertilization secondary oocytes complete meiosis II to form mature oocytes and second polar body
- √ So fertilization give us: mature oocytes and 2<sup>nd</sup> polar body

## Male Gametogenesis

### Spermatogenesis:

- Spermatogenesis, which begins at puberty, include all of the events by which spermatogonia are transformed into spermatozoa
- Spermatogenesis = Spermatocytogenesis + Spermiogenesis
- Spermatogenesis is regulated by Luteinizing hormone (LH) production by the pituitary. LH binds to receptors on Leydig cell and stimulates testosterone production, which in turn binds to Sertoli cell to promote spermatogenesis. FSH is also essential for spermatogenesis
- Spermatogenesis requires about 74 days, together with transportation, a total of about 3 months elapse before sperm ejaculated
- The X chromosome appears to be important for spermatogenesis.

### Spermatocytogenesis:

- Primordial germ cell:
- ✓ Primordial germ cell from the wall of yolk sac arrive in the testis at week 6<sup>th</sup> of

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### Type A spermatogonia:

- ✓ Primordial germ cell at puberty differentiate into type A spermatogonia
- ✓ Type A spermatogonia undergo mitosis to provide a continuous supply of stem cells throughout the reproductive life of the male(called Spermatocytogenesis)
- ✓ The undifferentiated germ cell, found in the basal compartment of the somniferous tubules are called type A spermatogonia
- ✓ Type A spermatogonia are the only true stem cell in the testis because they can either self-renew or differentiate to become sperm.

### Type B spermatogonia:

- ✓ Some type A spermatogonia differentiate into type B spermatogonia.
- ✓ Type B spermatogonia enter meiosis-l and undergo DNA replication to form-Primary spermatocytes complete meiosis 1 to form two-----secondary spermatocytes------These secondary spermatocytes complete meiosis-II to form four haploid spermatid

### Spermiogenesis:

Spermatid undergo a postmeiotic series of morphological changes to form sperm and this process is called Spermiogenesis



### **Female Reproductive Cycle**



### Ovarian cycle

### a) Follicular phase:

- Oogonia-----Primary oocyte(There are approximately two million primary oocytes in the ovaries of a newborn female, but most regress during childhood so that by adolescence no more than 40,000 remain.)-----Primordial follicle-----Primary follicle----Growing follicle or secondary follicle
- Primordial follicle---Single layer of squamous/flat cell around the oocyte
- Primary follicle---layer of Cuboidal Granulosa cell around the oocyte, Granulosa cell secret estrogen. FSH, causes accelerated growth of 6-12 primary follicles each month
- Secondary follicle
- Formation of Zona pellucida:
  - ✓ The follicle cells deposit some homogenous material on the surface of the oocyte, which contains glycoprotein. This layer gradually thickened to form zona pellucida which is the acellular layer
- · Formation of thica interna and thica externa:
  - ✓ It is connective tissue around the ovarian follicles.
- Formation of follicular cavity:
  - ✓ In follicles, irregular space appears between folliculars cell which later on joins each other to form a cavity called follicular cavity or follicular antrum.

### Formation of Graffian follicle:

- The follicular cavity becomes crescent-shaped and filled with follicular fluid, which contains estrogenic hormones. The follicle now matured and called Graffian follicle
- ✓ The follicular cell surrounding the oocyte are called Cumulus oophorus. At ovulation, some of cumulus oophorus cell surrounding the ova leave the Graffian follicle and are

called corona radiate.

Corona radiate originate from squamous Granulosa cells present at the primordial stage of follicular development

### b) Ovulatory phase:

- Ovulation is the release of ovum from a mature Graffian follicle, which occurs in the middle of each ovarian cycle. This process is under the influence of LH surge
- Just 2 day before ovulation, the rate of secretion of LH by the anterior pituitary gland increases markedly and peaking about 16 hours before ovulation

### c) Luteal phase

- This phase follows ovulation and during it the ruptured Graffian follicle transforms into the yellowish body called corpus luteum
- The corpus luteum secret a hormone called progesterone
- This hormone is responsible for the endometrial growth of the fertilized egg and maintenance of the endometrial layer of the uterus

### If fertilization does not occur:

- o The corpus luteum lives for 9-12 days only, decrease in size and degenerate into corpus luteum of menstruation.
- o The corpus luteum consequently transforms into a white scar called corpus Albicans

#### If fertilization occurs:

- The embryo secret HCG, which stimulates the growth of corpus luteum for form a large structure, called corpus luteum of pregnancy.
- The function of corpus luteum of pregnancy is to secret progesterone until the end of 4th months, after which placenta takes over this function and corpus luteum degenerate

### Menstrual cycle

#### a) Menstrual Phase:

- In this stage, bleeding per vagina occur which is termed as menstruation.
- During this phase, the superficial layer of the endometrium (entire compact and most spongy layer) shed off and excreted through the vagina.
- Cause of menstruation is hormonal withdrawal

### b) Proliferative Phase

- The phase starts from the end of menstrual flow until ovulation and occurs under the influence of estrogen. Following changes occur in uterus and ovary
  - ✓ Ovary: Primordial follicle convert into Graffian follicle
  - ✓ Uterus: blood supply of uterus increase as a result of which the uterus becomes spongy

### c) Ovulation:

- \* At mid-cycle i.e. 14, the expelled oocyte is drawn into the fallopian tube and begin journey
- Mittelschmerz and Ovulation: A variable amount of abdominal pain, mittelschmerz (German, mittel, mid + schmerz, pain), accompanies ovulation in some women. In these cases, ovulation results in slight bleeding into the peritoneal cavity, which results in sudden

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constant pain in the lower abdomen. Mittelschmerz may be used as a symptom of ovulation, but there are better symptoms, such as the slight drop in basal body temperature.

### d) Secretory phase:

- It starts after ovulation and continuous up till the beginning of menstruation occurs under the influence of progesterone which is produced by the corpus luteum of the ovary.
- In secretary phase following changes occur in ovary and uterus
  - ✓ Ovary: after ovulation, griffin follicle degenerates to form corpus luteum and start secreting progesterone
  - Uterus: the endometrium thickens, becomes more tortuous and filled with secretion. Spiral arteries grow into the spongy and compact layer of endometrium

### e) Ischemic phase:

- If fertilization does not occur, the ischemic phase begins
- Estrogens and progesterone levels drops
- Corpus luteum degenerate
- Spiral arteries become constricted
- Venous stasis and ischemic necrosis
- \* Shrinking of endometrium, with patchy ischemic necrosis, resulting in bleeding in the uterine cavity

### Clinical notes:

Cessation of menstruation is often the first indication that a woman may be pregnant. Approximately 3 weeks after conception, approximately 5 weeks after the last normal menstrual period, a normal pregnancy can be detected with Ultrasonography

### Human Chorionic Gonadotropin (hCG)

- Human chorionic Gonadotropin is glycoprotein composed of 237 amino acids with a molecular mass of 36.7 (30-40) kDa
- " it is heterodimeric, with an α (alpha) subunit identical to that of luteinizing hormone (LH), folliclestimulating hormone (FSH), thyroid-stimulating hormone (TSH), and B (beta) subunit that is unique to hCG.
  - The α (alpha) subunit is 92 amino acids long. Not a tumor marker
  - ✓ The β-subunit of hCG Gonadotropin (beta-hCG) contains 145 amino acids
- It is produced by the Syncytiotrophoblast that stimulated the production of progesterone by the corpus luteum of the ovary
- During the last 7<sup>th</sup> month hCG is formed by placenta
- HCG can be assessed in maternal blood at day 9-8 or maternal urine at day 10 and is the basis of pregnancy testing
- HCG is detectable throughout pregnancy
- hCG's primary role is to keep the corpus luteum functioning, so that the corpus luteum continues to produce estrogen and progesterone and thereby maintaining hormonal support to pregnancy

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- Allantois appears on day 16 as a small sausage-shaped diverticulum from the caudal end of the yolk sac, which extends into the connecting stalk
- The Allantois involve in the early formation and development of urinary bladder
- As the urinary bladder develops the Allantois become Urachus, which is represented in adult by the median umbilical ligament
- · Can form, cyst, fibrous band, sinus or fistula but can't form a polyp
- Urachus:
  - Urachus is duct between fetal bladder and umbilicus
- Patent Urachus: failure of Urachus to obliterate---urine discharge from umbilicus
- Median umbilical ligament----which connect the apex of the bladder to the umbilicus
- Urachal cyst—it is the remnant of Allantois

### **Early Fetal Development**

Day 0	<ul> <li>Fertilization by sperm forming zygote, initiating embryogenesis</li> </ul>
Within week 1	<ul> <li>hCG secretion begins after implantation of the blastocyst</li> </ul>
Within week 2	Bilaminar disc (epiblast, hypoblast)2 weeks
Within week 3	<ul> <li>Trilaminar disc 3 weeks = 3 layers</li> <li>Gastrulation</li> <li>Primitive streak, notochord, mesoderm and its organization and neural plate begin to form</li> </ul>
Weeks 3-8 (embryonic period)	A Neural tube formed by Neuroectoderm and closes by week 4     Organogenesis     Extremely susceptible to teratogens
week 4	<ul> <li>The Heart is formed and begins to beat but the heart tube is formed at the age of 17 days</li> <li>Upper and lower limbs buds begin to form</li> <li>4 weeks = 4 limbs, 4 chambers of the heart</li> </ul>
Week 8 (start of fetal period)	Fetal development, fetus look like a baby
Week 10	The genitalia have male/female characteristics

### Important Term

- 1) Trophoblast: It differentiates into two layers
  - Cytotrophoblast
  - Syncytiotrophoblast
- 2) Embryoblast: Form two layers
  - Epiblast
  - Hypoblast
- 3) Cleavage:

- Series of mitotic cell division in the zygote at the fallopian tube to increase the number of cells. These cells are known as Blastomeres
- Once the zygote reached the two-cell stage, it undergoes a series of mitotic division. increases the number of cells.
- These cells, which becomes smaller with each cleavage division are known as Blastomeres

### 4) Compaction:

After 3<sup>rd</sup> cleavage, Blastomeres maximize their contact with each other forming a compact ball of cells held together by tight junctions. This process is called compaction.

### 5) Morula:

- Cells of compacted embryo divide again to form 16 cell stage which is called Morula
- Morula still enveloped by zona pellucida
- Appearance: Mulberry appearance

### 6) Acrosome reaction:

 The sperm bind to the zona pellucida of the secondary oocyte arrested in metaphase of meiosis II and triggers Acrosome reaction, causing the release of acrosomal enzyme e.g. acrosin

### 7) Cortical reaction:

The Cortical reaction is the release of the lysosomal enzyme from cortical granules near oocyte cell membrane potential and inactivates sperm receptors on the zona pellucida

### 8) Capacitation:

 Newly ejaculated sperm are incapable of fertilization until they undergo Capacitation, which occurs in the female reproductive tract (uterus) and involves the unmasking of sperm glycosyltransferases and removal of proteins coating the surface of the sperm

### 9) Neurulation:

The Process where neural plate forms the neural tube

### 10) Gastrulation:

Process of formation of trilaminar germ disc(ectoderm, mesoderm, endoderm) in embryo

### 11) Implantation:

- The process during which the blastocyst attaches to the endometrium, the mucous membrane or lining of the uterus, and subsequently embeds in it. The preimplantation period of embryonic development is the time between fertilization and the beginning of implantation, a period of approximately 6 days.
- During implantation, uterus is in the Secretory phase

### Sperm



- . The main function of sperm is to transport male genes into to the female's egg
- After ejaculation sperm stored into the ampulla of ejaculatory duct
- Aspermia———Complete lack of semen
- \* Azoospermia-----Absence of sperm in the semen, (investigation of choice for Azoospermia is FSH and LH also check Sertoli cell function)
- \* Asthenozoospermia: Reduced sperm motility, there is a significant decrease in mobility after 45 years
- . Oligospermia: decreased number of spermatozoa in semen, less than 20million

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- Fertilin is a sperm surface protein with an essential role in fertilization. It is required for the migration of spermatozoa through the oviduct, for binding to the zona pellucida, and for efficient binding to the egg plasma membrane.
- Sperm reaching Epididymis, movement become directional
- Sperm contain vitamin C and fructose which give nourishment to sperm
- The average volume of semen per ejaculation -----2-6 ml
- . Human sperm cells consist of a flat, disc-shaped head 5.1 μm by 3.1 μm and a tail 50μm long. The tail flagellates, which propels the sperm cell (at about 1-3 mm/minute in humans) by whipping in an elliptical cone.
- Total sperm produced by two testes per day-----120million
- Total sperm per-ejaculate 400 million/ejaculate or 120million/ml
- Total number of mature sperm 100million/ejaculate or 20million/ml
- For a person to be fertile sperm count should be at least 20million/ml
- Sperm spend 45 to 60 days developing in the testis and 2 to 12 days in the epididymis.
- Sertoli cells produce inhibin, which inhibits FSH, and activin, which stimulates FSH.
- Parts of sperm:
  - ✓ Head-----largest part, contain DNA
  - Middle Piece-----contain mitochondria to make ATP and pair of the centriole, the only centriole are donated to the oocyte. The middle segment of sperm is highly organized, consisting of helically arranged mitochondria that surround a set of outer dense fibers and the 9 + 2 microtubular structure of the axoneme. The sperm head contains an acrosome and the nucleus, and the tail contains the axoneme.
  - ✓ Tail----longest part, flagellum provides movement for sperm

### Placenta



- The definitive placenta is formed at 4 months
- All drugs absorb by carrier-mediated mechanism
- Glucose is absorbed into fetal blood by facilitated diffusion
- Fatty acid are absorbed into fetal blood due to lipid-solubility
- Amino acids, PO<sup>4</sup>, Ca<sup>++</sup> and vitamin-c are absorbed into fetal blood by active transport
- Ketone bodies, Na<sup>+</sup>, K<sup>+</sup> and Cl<sup>-</sup> are absorbed into fetal blood due to concentration gradient Estrogen and progesterone produced by the placenta in the third trimester
- Placenta attach to the uterus at the posterosuperior surface
- Blood leaves the placenta by umbilical vein
- Things that can cross placenta:
  - ✓ Anti-D and IgG
  - ✓ Thyroxin
  - ✓ Gallamin is a neuromuscular blocker can also cross the placenta
  - √ Warfarin
- The Placenta is the physiological barrier between fetal and maternal blood
- The Placenta is the fetomaternal organ
  - ✓ The fetal portion is known as-----Tertiary chronic villi (chorionic frondosum)

✓ The maternal portion is known as—Decidua basalis

### 1. Decidua:

At the implantation location, the maternal endometrium is changed by a decidual reaction and is called the deciduas. Types

- ✓ Decidua basalis
  - o Forming the maternal component of the placenta
- ✓ Decidua capsularis
  - Superficial portion overlying the Conceptus
  - O Obliteration of uterine cavity occur due to fusion of deciduas parietalis and deciduas capsularis
- ✓ Decidua parietalis
  - o All the remaining uterine mass



### **Amniotic Fluid**



- The fluid present in the amniotic cavity is called amniotic fluid
- \* Volume: 500-1000ml
- Function:
  - ✓ Acts as a shock absorber
  - ✓ Regulates temperature of the fetus
  - ✓ Protects fetus from the strong muscular contraction of the uterus

### Amniotic band syndrome:

Amniotic band syndrome can occur when the inner layer of the placenta, called the amnion, is damaged during pregnancy. If this happens, thin strands of tissue (amniotic bands) form inside the amnion. These fiber-like bands tangle around the developing fetus, restricting blood flow, thus affecting the growth of certain body parts. In some cases, strands can tangle so tightly around the limbs of a fetus that they amputate them.

### Sertoli Cell Vs Leydig Cell

<u>S</u> ertoli cell		Leydig cell	
	Sertoli-Sertoli tight junctions are the strongest cell-cell interactions in the body and give the blood-testis barrier its name.	The state of the s	
	Temperature-sensitive cell	<ul> <li>Not affected by temperature</li> </ul>	
*	FSH act here	<ul> <li>Secretion is stimulated by <u>L</u>H</li> </ul>	
Function:  ✓ Antimüllerian which cause atrophy of Müllerian duct ✓ Inhibin: inhibit FSH ✓ Androgen binding protein: maintain the local level of testosterone ✓ Support, protect and nourish the spermatogenic cells		<ul> <li>Contain abundant SER</li> <li>These cells mature and begin to secret during puberty</li> <li>Interstitial cell of Leydig are round to polygonal in the interstitial regions between seminiferous tubules</li> </ul>	

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Embryonic structure	Remnants	
Yolk sac	<ul> <li>Vitelline duct (persist as Meckles diverticulum)</li> </ul>	
Gubernaculum	ovarian ligament and the round ligament of the uteru in the female	
<ul> <li>Process vaginalis</li> </ul>	Male: tunica vaginalis, Female: canal of Nuck	
<ul> <li>Thyroglossal duct</li> </ul>	foramen cecum	
<ul> <li>Left Umbilical vein</li> </ul>	Ligamentum teres	
<ul> <li>Right umbilical vein</li> </ul>	Disappear in the umbilical cord	
<ul> <li>Umbilical arteries</li> </ul>	Medial umbilical ligament	
<ul> <li>AllaNtois</li> </ul>	MediaN umbilical ligament	
Ductus arteriosus	<ul> <li>Ligamentum arteriosum (connect aorta with lef pulmonary artery</li> </ul>	
<ul> <li>Ductus venosus</li> </ul>	Ligamentum venosum	
<ul> <li>Foramen oval</li> </ul>	Fossa ovalis, foramen oval close soon after birth	
<ul> <li>Notochord</li> </ul>	Nucleus pulposus of Intervertebral disc	
	<ul> <li>Unlike the median and medial umbilical folds, the contents of the lateral umbilical fold remain functional after birth. It contains inferior epigastric vessels. And is is not the embryological or developmental remnant</li> </ul>	
1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Congenital Malformation	
Syndactyly	Fusing of finger, most often occurs between middle and ring finger	
Brachydactyly	Short of finger or toes	
Polydactyly	The Situation where there are more than the usua	
	number of digits (five) in a hand or foot.	
Sirenomelia	The fusion of both leg and there is no feet	
Renal agenesis	Absence of one or both kidney	
Dextroposition of heat	Denote a heart on right side	
Microcephalous	Small head	
Anencephalus	failure of the anterior neuropore to close, the brain doesn'	
	develop, incompatible with life	
Encephalocoele	The herniation of brain through the cranial structure	

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Ectoderm	Mesoderm	Endoderm
 Epidermis, hair, nail, sweat gland and sebaceous gland Adenohypohysis  Epithelial lining of Lower anal canal The Distal part of the urethra External auditory meatus	<ul> <li>Muscle (smooth, cardiac and skeletal muscle)</li> <li>The Muscle of tongue (occipital somites)</li> <li>Pharyngeal arch muscles</li> <li>Connective tissue</li> </ul>	<ul> <li>Hepatocyte</li> <li>Acinar and islet cells of the pancreas</li> </ul>
 Neuroectoderm  All neuron Retina, Optic nerve Dilator and sphincter papillae muscle Astrocytes, Olgiodendryocytes, ependymocytes, tanycytes, choroid plexus Neurophysins Pineal gland	<ul> <li>Dermis and subcutaneous layer of skin</li> <li>Bones and cartilage</li> <li>Dura matter</li> <li>Endothelium of blood vessels</li> <li>RBCs, WBC,s microglia and kupffer cell</li> <li>Kidney</li> <li>Adrenal Cortex</li> </ul>	<ul> <li>Epithelial lining of:</li> <li>Gl tract</li> <li>Trachea, bronchia, lungs</li> <li>Billary apparatus</li> <li>Urinary bladder</li> <li>Female urethra</li> <li>Most of male urethra</li> <li>Inferior 2/3 of the</li> </ul>
 Neural crest  Neuron within ganglia (dorsal root, cranial, autonomic)  Schwan cell  Adrenal medulla  Melanocytes  Aorticopulmonary septum  Bones of the neurocranium  Pharyngeal arches bones  (maxilla, mandible, malleus and	<ul> <li>Notochord</li> </ul>	vagina  Auditory tube, middle ear cavity  Mesentery Palatine tonsil Thyroid follicle

Partial List Of Carry	
Control Cist Of Germ	Laver Derivatives—V V INAR
THE REAL PROPERTY OF THE PERSON NAMED IN COLUMN TWO IS NOT THE PERSON NAMED IN COLUMN TWO IS	Layer Derivatives—V-V-IMP

High-Yield Points		
At term	CRL:36 cm and CHL: 50 cm	
Head of the fetus becomes exactly half the length at CRL	3 <sup>rd</sup> months	
CRL used between	7 - 14 weeks	
BPD is used	16 - 30 weeks	
Sperm life in genital tract stay active for	24 to 48 hours (1-2 days)	
Sperm life span	24-72 hours	
The Prenatal chromosome is detected at	14 -18 weeks	
Embryonic period (period of organogenesis)	3-8 weeks	
Fetal period	The Period after 8 weeks	
At birth in the umbilicus	2 umbilical arteries present	
Compaction and segregation of inner cellular mass occur after		
Incidence of Down syndrome increase with	Advance Maternal age	
Incidence of achondroplasia increase with	Advanced Paternal age	
Fetal cardiac activity detected by transvaginal Ultrasound by:	6 week	
Fetal cardiac activity detected by trans-abdominal U/S by:	7 Weeks	
Fetal movement detected by the mother at:	20 weeks	
Fetus start movement at:	8 Weeks	

### **Somites**

- Somites are derived from paraxial mesoderm and develop on both side of the notochord
- The first pair of somites arise in the occipital region of the embryo at approximately the 20 the day of development
- From here, new somites appear in craniocaudal sequence at a rate of approximately three pairs per day until the end of the 5<sup>th</sup> week
- They can't be counted and are used to roughly estimate the age of the embryo
- The first occipital and the last five to seven Coccygeal somites later disappear
- Number of somites in the cervical region: 4 Pairs

Approximate age (D)	Number of Somites
20	1-4
21	4-7
22	7-10
23	10-13
24	13-17
25	17-20
26	20-23
27	23-26
28	26-29
30	34-35

incus)

## Chapter 24

### Embryology

NASEEM SHERZAD FCPS -1 HIGH-YIELD

## Adult Derivatives of Pharyngeal Arches

- There are 6 mesodermal thickenings on both side of the pharynx
- They appears in the 4<sup>th</sup> and 5<sup>th</sup> weeks
- Arches are covered with ectoderm externally and lined with endoderm internally
- Arches are separated from each other by 4 clefts on the outer surface which is covered with
- Arches are separated from each other by 5 pouches on the inner aspect(cavity of the pharynx) which are lined with Endodermal layer
- 1) Ist arch-----Chew-----Words with M
  - Malleus and incus
  - Sphenomandibular ligament
  - Trigeminal (V) nerve (Maxillary and Mandibular divisions only)
  - Muscles::
    - ✓ Muscles of Mastication
    - Mylohyoid and anterior belly of the digastric
    - Tensor tympani
    - ✓ Tensor veli palatini
  - Abnormalities: Treacher collins syndrome-------Ist arch neural crest fails to migrate---mandibular hypoplasia, facial abnormalities
- 2) 2<sup>nd</sup> arch------Smile-----words with S
  - Stapes, Styloid process and Stylohyoid ligament
  - lesser cornu and the Superior part of the hyoid bone
  - Facial (VII) nerve
  - Muscles:
    - ✓ Muscles of facial expression
    - ✓ Stapedius
    - ✓ Stylohyoid
    - ✓ Posterior belly of the digastric
- 3) 3rd arch
  - Greater cornu and inferior part of the body of the hyoid bone
  - Glossopharyngeal (IX) nerve
  - Stylopharyngeus muscle
- 4) 4th arch
  - Most pharyngeal constrictors, Cricothyriod, levator veli palatini
  - CN X-----superior laryngeal branch
- 5) 6th arch
  - All intrinsic muscle of larynx except Cricothyriod
  - CN X----recurrent laryngeal branch
  - 4th and 6th branchial arch cartilages fuse to form the laryngeal cartilages, except for the epiglottis which forms from the mesenchyme in the hypobranchial eminence (from the 3rd and 4th branchial arches).

## PHARYNGEAL POUCHES

Develop between the Branchial arches (1st pouch is found between the first and second Branchial arches). There are 4 pairs, the 5th is absent or very small.

. The endoderm of the pharyngeal pouches and the ectoderm of the branchial grooves contact each other to form the branchial membranes separating the pharyngeal pouches and the branchial grooves.

- Derivatives of the pharyngeal pouches
- 1) 1st pharyngeal pouch:
  - The Epithelial lining of auditory tube and middle ear cavity
- pharyngeal pouch
  - The Epithelial lining of palatine tonsil crypts
- 3) 3rd pharyngeal pouch---IT
  - Inferior parathyroid gland
  - Thymus
- 4) 4th pharyngeal pouch
  - Superior parathyroid gland
  - Ultimobranchial body

### Difference between Chorionic Villus Sampling and Amniocentesis

- Chorionic Villus Sampling(CVS):
  - Performed between ------10-14 weeks of conception
  - Indications:
    - Prenatal diagnosis of Thalassemia and Child sex
    - ✓ Increase nuchal translucency or other abnormal ultrasound findings
    - ✓ Advanced maternal age (maternal age above 35)
    - ✓ Abnormal first-trimester screen result
    - ✓ Fetal DNA can also be used for karyotyping
    - Can detect more than 200 different types of the genetic and biochemical condition:
      - o Down syndrome
      - o Cystic fibrosis
      - o Tay-Sachs disease
- 2) Amniocentesis:
  - Performed:-----after 15 weeks-----15-21 weeks
  - Indications:
    - ✓ Rh incompatibility
    - ✓ Decompression of Polyhydramnios
    - ✓ Can predict fetal lung maturity
    - ✓ Infection, in which amniocentesis can detect decrease glucose level, a Gram stain showing bacteria or an abnormal differential count of WBC
  - Complication:
    - ✓ Preterm labor and delivery
    - ✓ Respiratory distress
    - ✓ Postural deformities, Chorioamnionitis, fetal trauma and alloimmunization of the mother (rhesus disease)

NASEEM SHERZAD FCPS -1 HIGH-YIELD

- Cell division occurs during this phase
- In this one cell splits into two new cells
- Occurs after replications of DNA and chromosome.
- The daughter cell contains the same number of the chromosome as in parent cell
- Shortening of chromosome in mutation, the enzyme responsible for it is telomerase
- The main difference between centromere and kinetochore is that centromere is the region where the two sister chromatids are held together after the replication of chromosome where kinetochore is the protein complex on the chromosome where spindle fibers are attached during cell division
- It has 6 stages --- PM-ATC

### 1. Prophase:

- ✓ The first and longest stage of mitosis
- ✓ In this stage, the chromosomes become visible and the centrioles separate and move to opposite poles of the cell.
- ✓ Chromosome first appear in prophase
- Chromosome appear as 2 identical sister chromatids joined together at the centromere

### 2. Prometaphase:

- ✓ The nuclear envelope disrupted, giving the microtubules access to the chromosome.
- ✓ The nucleolus disappears

### 3. Metaphase:

- In this stage, the chromosomes line up across the center of the cell and become connected to the spindle fiber at their centromere.
- Chromosome arrange on equatorial pole
- ✓ Pairing of chromosome
- ✓ Chromosome thickest
- ✓ Chromosome karyotyping or chromosomal study done during this phase
- ✓ The Cell can be arrested by microtubules inhibitors (e.g. colchicine)

### 4. Anaphase:

✓ In this stage, the sister chromatids separate into individual chromosomes and are pulled apart.

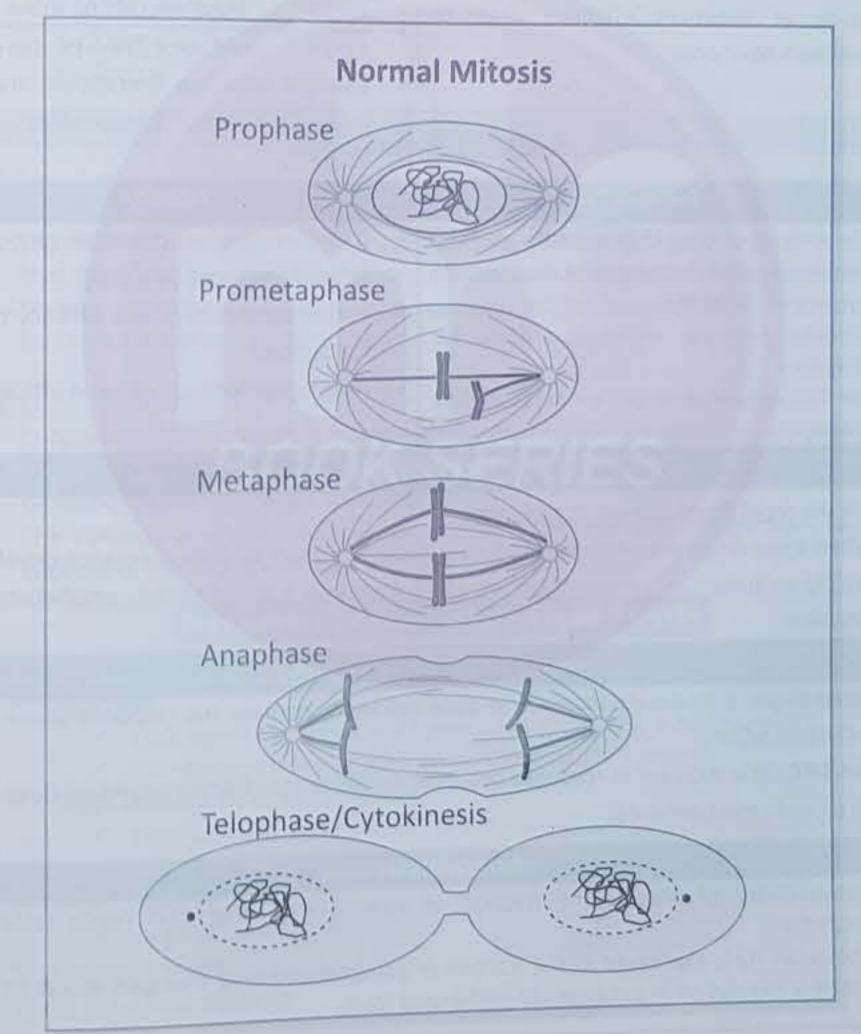
### 5. Telophase:

- ✓ During this stage, the chromosomes gather at opposite ends of the cell and lose their distinct rod-like shapes. Two new nuclear membranes then form around each of the two regions of DNA and the spindle fibers disappear.
- ✓ Two separate sister chromatids formed and two separate cells formed
- ✓ Chromosome decondense to from chromatin
- ✓ Nucleolus reappear

- 6. Cytokinesis:
  - ✓ Cytoplasm divide through the process of cleavage.
  - ✓ A cleavage furrow form around the center of the cell
  - ✓ A contractile ring form at the cleavage furrow. The ring is composed of actin and myosin filaments

### 7. Difference between mitosis and meiosis:

- ✓ Mitosis results in two identical daughter cells, whereas meiosis results in four sex cells.
- Chromosomes exchange genetic material during melosis in a process called crossing over.
- ✓ In mitosis, Daughter cells are genetically identical whereas in meiosis Daughter cells are genetically different



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### **Important Terms**

Therapeutic Window	Therapeutic Index
<ul> <li>The Measure of clinical drug safety</li> <li>Range of minimum effective dose to minimum toxic dose</li> </ul>	<ul> <li>The Measure of drug safety</li> <li>LD50 median lethal dose</li> <li>ED50 median effecive dose</li> <li>Example with low therapeutic index: digoxin, lithium, Theophylline and warfarin</li> </ul>
Potency	Efficacy
<ul> <li>The amount of drug that must be given to produce a particular response is called the potency of the drugs</li> <li>Increase potency, increase affinity for receptors</li> <li>The Therapeutic dose can be measured by potency</li> </ul>	<ul> <li>It refers to the maximal response (effect) produced by a drug</li> <li>Partial agonist have less efficacy than full agonist</li> <li>All antipsychotic are same in efficacy</li> </ul>

### **Tachyphylaxis**

- It is the rapid development of tolerance
- When some drugs are administrated repeatedly at a short interval, tolerance develops rapidly as known as tachyphylaxis or acute tolerance e.g. ephedrine, amphetamine, tyramine

### Dose-Response Curve (DRC)

- Steep slope: a moderate increase in dose markedly increase the response (dose not individualization)
- Flat DRC: little increase in response occurs in a wide range of doses (standard dose can be given to most patients)

### Bioavailability

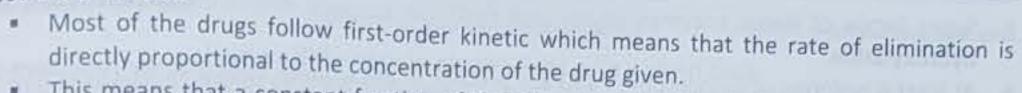
- Bioavailability of drug is the fraction of administered drug that reach systemic circulation
- Bioavailability is expressed as the fraction of administered drug that gain access to the systemic circulation in a chemically unchanged form

Chapter 25 :

## NASEEM SHERZAD FCPPharmacology

Kinetic of Clearance

### First-order kinetic:



This means that a constant fraction of the drug present in the body is eliminated in a unit time. Therefore increasing the dose or concentration, increase the elimination and a decrease in the dose causes a decrease in elimination till the elimination is complete

### Zero-order kinetic:

- A few drug follow zero order-kinetics, which means a fixed quantity, not a proportion of any concentration is eliminated per unit time, which implies that the rate of elimination is constant irrespective of the quantity of the drug given
- Zero-order elimination----PEA zero
  - Phenytoin
  - Ethanol
  - ✓ Aspirin



#### Drug Metabolism



### Phase I:

- Reduction, oxidation, hydrolysis and hydroxylation by Cytochrome P-450 usually yield slightly polar, water-soluble metabolites (often still active)
- ✓ Hydroxylation by Cyt.P450: hydroxylation is the chief reaction involved in phase-1. The responsible enzyme is called monooxygenases or Cytochrome P450s
- ✓ Geriatric patient loss phase 1 first

### A Phase II:

- Conjugation (Methylation, Glucuronidation, Acetylation, Sulfation) usually yield very polar, inactive metabolites (renally excreted)
- ✓ Geriatric patient have More GAS (phase II)
- ✓ The Patients who are low acetylators have increased side effects from certain drugs because of the decrease rate of metabolism

### Naseem Sherzad High-Yield Points

- Drugs causing peripheral neuropathy and pancreatitis---diadnosine
- Opacities
  - ✓ Lens opacities-----caused by-----Chlorpromazine > Amiodarone
  - ✓ Corneal opacities—caused by——Chloroquine > copper
- Drugs induced Thrombocytopenia:
  - ✓ Quinidine and quinine———commonest
  - ✓ Sulfonamide
  - √ Ranitidine
  - ✓ Heparin and Vancomycin
- Chlorpromazine:
  - √ Cause dystonia

### Cytochrome P-450

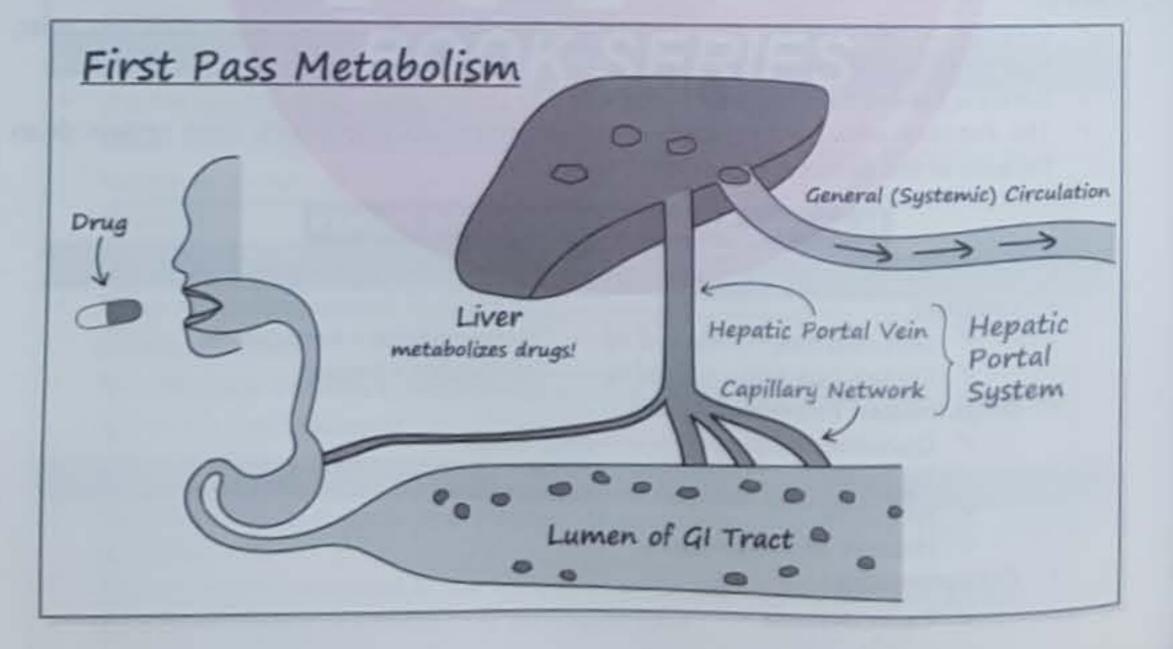
- Super family of Heme enzymes (many isoforms) can catalyze different reaction types, mainly hydroxylation.
- At least 6 isoforms of Cytochrome P450 are present in the smooth endoplasmic reticulum of the human liver (highest amount present in liver)
- Acting on both Xenobiotics and endogenous compound
- It Can be induced and inhibited. Most of the isoforms of Cytochrome P450 are inducible
- Inducers
  - √ Phenobarbital
  - Dexamethasone
  - ✓ Rifampin

### Inhibitors: I-COKE

- √ Isoniazid
- Cimetidine
- Omeprazole.
- Ketoconazole
- Erythromycin
- √ Valproate
- √ Grapefruit juice

### First Pass metabolism:

- The first pass effect (also known as first-pass metabolism or presystemic metabolism) is a phenomenon of drug metabolism whereby the concentration of a drug, specifically when administered orally, is greatly reduced before it reaches the systemic circulation.
- ✓ First pass metabolism can be avoided if drug given: IV> Sublingual> I.M>> Per-rectal



Chapter 25

Pharmacology

### Drug Interactions

### Pharmacokinetic Interactions

## Cause a difference in plasma level with a given dose

### During absorption: These may occur in the

- Lumen and are called direct interaction e.g.
  - Tetracycline or iron given with antacid----cause formation of insoluble compounds
  - ✓ Cholestyramine given with thyroxine or digoxin——also form insoluble complexes
  - ✓ Similarly, Sucralfate and Phenytoin given concurrently can cause the formation of insoluble compounds

### Due to alteration in the gut flora

✓ Antimicrobials (which inhibit the bacterial synthesis) given with oral anti-coagulants, may cause bleeding

### · Motility changes:

- ✓ The Anti-Muscarinic drug given with morphine——decrease its absorption
- ✓ Purgative given with steroids or digoxin decrease the time for absorption

### Absorptive through other than oral route:

- Hyaluronidase with S/C drug help in spreading
- √ Vasoconstrictors with S/C drugs, prolong local anesthetic effect.

### Interactions during distribution: these are of three types

### During protein binding

- ✓ Sodium valproate given along with Phenytoin sodium, displace Phenytoin sodium. from its protein binding and inhibits its metabolism, thus increasing its efficacy
- ✓ Aspirin or Probenecid given with methotrexate, displace methotrexate from its binding site and also decrease its elimination through inhibiting active secretion ------ causing its toxicity
- ✓ Sulfonamide or indomethacin, displace the protein-bound Bilirubin, causing kernicterus

#### Direct in blood

- ✓ Protamin given with heparin, antagonize it
- ✓ Deferoxamine given with iron, antagonize it
- Dimercaprol antagonizes arsenic

### During tissue binding

- Quinidine displace digoxin -----leading to toxicity
- ✓ On receptors may be:
  - Wanted: like naloxone given to interact with morphine receptors
- ✓ On body system:
  - Different CNS depressant, augment each other dressing effects
  - Verapamil given with beta-blocker, causes bradycardia or heart block
  - O Thiazide diuretic given with lithium, cause lithium toxicity

### Interaction during metabolism:

- ✓ Enzyme induction
  - Chronic alcohol ingestion, increase the rate of metabolism of tolbutamide
  - Enzyme inducing agent phenobarbitone increase the metabolism of warfarin, necessitating an increase in its dose
  - Phenytoin given with oral contraceptive, may cause contraceptive failure

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### ✓ Enzyme inhibition

- o Na-valproate decrease the metabolism of Phenytoin-Na
- Cimetidine decrease the metabolism of propranolol, can cause heart block
- Allopurinol, inhibiting xanthine oxidase, decrease the rate of metabolism of azathioprine and mercaptopurine

### Interaction during excretion

- During active excretion
  - Alkalinization increase the excretion and ionization of Salicylates and phenobarbitone (acidic drug)
  - ✓ Ammonium chloride, increase the ionization and excretion of amphetamine(basic drug)
- During passive excretion
  - Quinidine decrease the secretion of digoxin
  - Aspirin decrease the secretion of methotrexate
  - Probenecid decreases the excretion of penicillin
  - Probenecid also decreases the excretion of zidovudine

### Pharmacodynamic Interactions

Bring about the difference in the effect of the drugs by a given plasma level. These may be of the following types

### Addition:

When the response is equal to the combined response of the individuals drugs (1+1=2) e.g. ethanol given with diazepam doubles the depressing effect on CNS

### Synergism:

When the response is greater than the algebraic sum of the individual response (1+1=3) e.g. Trimethoprim + sulfamethoxazole

### Potentiation:

- When a drug having no effect of its own, enhance the effect of a  $2^{nd}$  drug(0+1=2)
- Benserazide + Levodopa, clavulanic acid + Amoxicillin
- Antagonism: When a drug inhibits the effect of another drug. It may be
  - a) Acting on the same receptors: isoprenaline + Beta-blocker. The inhibition may be:

### Competitive

- These cause a parallel shift of the dose-response curve to the right. The effect may be the same
- o Tubacurarine-----inhabiting acetylcholine
- o Propranolol-----antagonizing noradrenaline or adrenaline
- o Naloxone----inhibiting morphine
- Non-competitive: in which antagonist binds irreversibly to receptors to the site or to other sites inhibiting response to the agonist e.g. phenoxybenzamine+ adrenaline. These cause a non-parallel shift of the dose-response curve to the right. The effect is also decreased

### b) Acting on different receptors:

✓ Adrenaline (on alpha receptors) given to antagonize the effect of histamine (on Hi receptors) in anaphylactic shock

Chapter 25

Pharmacology

# Pre-operative Medication MOA and Modification of pre-existing drugs

- Cimetidine------Decrease gastric secretion
- Antibiotics------Given on table of surgery
- Atropine------Reduce respiratory secretion
- After cardiac surgery, major operation will be postponed for-----3-6 months
- Smoker should be encouraged to stop smoking 30 days (4-Weeks) before surgery
- Warfarin should be stopped 5 days before surgery
- Consider stopping of estrogen containing oral contraceptive or hormonal replacement therapy 4 weeks before surgery
- Traditionally, Monoamine oxidase inhibitors (MAOIs) are discontinued two weeks before elective surgery
- Oral hypoglycemic (Metformin) 48 hours (2 days) before surgery and switch to insulin
- Lithium-----stopped 24 hour prior to surgery
- ACE inhibitors and receptors blocker often omitted 24 hours (1 day) prior to surgery
- · Patient are advised not to take solids within 6 hours and clear fluid within 2 hours before anesthesia to avoid the risk of acid aspiration syndrome
- Hair is best removed by clipping immediately before surgery
- Patient with chronic End-stage renal disease should undergo dialysis before surgery as well as on the day after surgery
- Hold NSAIDs for 24-72 hours (1-3 days) preoperatively

### Drug of choice in Pregnancy

- Pregnancy-induced HTN------Labetalol >>> Methyldopa
- Pre-eclampsia or hypertensive emergency/urgency-------Hydralazine
- Treatment of choice for severe preeclampsia to prevent eclampsia, or after eclampsia develops to prevent more seizures: MgSO4 (given IV)
- Seizure in pregnancy------MgSO4
- Calcium gluconate does not affect the serum potassium level but counteract the myocardial effect of hyperkalemia
- Calcium gluconate is the antidote for Magnesium Sulfate toxicity
- Calcium chloride(Cacl2) is 3 times more potent than calcium gluconate and is the antidote for overdose - magnesium sulfate IV---this should be on top in options
- The Safe drug in pregnancy: insulin, Fluoxetine, Co-amoxiclav and co-trimoxazole
- Diabetic patient----insulin
- PPI of choice in pregnancy-----Lansoprazole
- Pregnant women develop AFib in the first trimester of pregnancy----IV heparin

### **OPIOIDS and NSAIDs**

### Morphine

- Is an alkaloid obtained from opium
- Having lowest PKa
- . The effect is comparable with nalbuphine
- Use for pain relief of MI, carcinoma, terminal illness, obstetric procedure, reduce apneutic threshold and raising the pain threshold
- Its half-life (By I/M) is 2.5 hour
- No tolerance occur for meiosis and constipation
- Side effects: MORPHINE
  - ✓ Miosis
  - ✓ Constipation
  - ✓ Respiratory depression (higher concentration of morphine remain in CSF for longer period of time as a result morphine is much more likely to reach the brain respiratory center and cause delayed respiratory depression than is Fentanyl or Sufentanil)
  - ✓ Urinary retention
  - √ Hypotension

### Pethidine

- Fast-acting, synthetic Opioids
- Less addictive
- Cause no cough suppression
- It has a short duration of action as compared to morphine
- Cause tachycardia in therapeutic doses
- It does not prolong labour but can cross the placental barrier
- MAO inhibitor using with pethidine can cause fetal excitation
- When concurrently given with MAO inhibitors, it can cause seizure, hyperpyrexia, hypertension
  and tachycardia and if given with SSRIs, it can cause serotonin syndrome

### Fentanyl

- It is a high potency Opioids
- It is a good anesthetic but not a good amnesic
- They also depress respiration
- Fentanyl has a therapeutic index of 270

### Chapter 25

### Pharmacology

- Irreversibly block platelet function
- Decrease elevated body temperature
- Low dose act on TXA2
- High dose act on Cyclooxygenase
- Overdose(2400-4000mg/day)---tinnitus
- Normal dose------Gl disturbance
- The Most common cause of increase bleeding time is aspirin ingestion
- Should be stopped 7-9 day before surgery, 10 days for clopidogrel
- AFib with TIA-----Warfarin
- Only TIA without Afib-----Aspirin
- Toxicity treatment: alkalization of urine, NaHCO<sub>3</sub> (MOA bicarbonate in aspirin poisoning is to increase excretion of aspirin through kidney)

Aspirin

- Acute Salicylates poisoning is more common in children.
- Serious toxicity occurs when the serum Salicylates level is more than 50mg/dl
- Aspirin poisoning:
  - √ Acid-base disturbance:
    - Ist respiratory alkalosis (low levels): direct effect on the CNS respiratory center and as a compensatory mechanism of metabolic acidosis
    - 2<sup>nd</sup> metabolic acidosis (high levels): depletion of HCO3, accumulation of salicylic acid derivatives, respiratory depression
    - 3<sup>rd</sup> mixed acidosis (Respiratory and metabolic)
  - ✓ Vomiting, Dehydration
  - √ Restlessness
  - √ Hyperpyrexia
  - √ Seizure
  - ✓ Coma and death

### Non-Steroidal Anti-Inflammatory drugs (NSAIDs)

- \* Ketorolac:
  - Analgesia is most preferable in-----Non-diabetic female undergoing cholecystectomy
  - For pain control of Asthmatic patient after cholecystectomy
  - Unlike OPOIDS Ketorolac has no effect on the CNS and has no sedative or anti-anxiety effect
- ❖ NSAIDs most suitable during lactation------Ibuprofen
- ❖ Most selective NSAID------Celecoxib

### **Three Syndromes**

- Chloramphenicol------ Gray-baby syndrome
- Amiodarone------Gray-man syndrome
- Vancomycin-----Red-man syndrome

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Pharmacology

### Chapter 25

### Pharmacology

### Endocrinology

### Propylthiouracil (PTU):

- MOA: Act by Inhibiting thyroid peroxidase to block iodine organification(addition of iodine to a tyrosine of thyroglobulin) and coupling reaction
- · Indication:
  - ✓ Use In IST trimester of pregnancy or when not mentioned first or 2<sup>nd</sup> trimester in the stem of BCQ
  - ✓ Thyroid crisis
  - ✓ For preparation before surgery.
  - ✓ Neonatal graves' disease
- 2<sup>nd</sup> trimester of pregnancy-----methimzzole (it is teratogenic, has the risk of embryopathy)

### Metformin:

- MOA—increase in insulin sensitivity, inhibit hepatic Gluconeogenesis
- Advantage: no hypoglycemia, cause weight loss
- Side effects:
  - Gl upset----Nausea and diarrhea
  - Lactic acidosis
  - Contraindicated in liver failure
  - Cause metallic taste in the mouth
  - ✓ Metallic taste is also caused by Metronidazole

#### Advantage:

- √ No hypoglycemia
- ✓ Weight loss

### Sulphonylureas:

- Drugs: Gliclazide, Glibenclamide, tolbutamide
- · MOA: Stimulate the release of insulin from the pancreatic beta-cell and so are only effective for a patient with some residual pancreatic function
- Indication: Type-2 DM inadequately controlled with dietary measures

### Usage:

- Can promote weight gain, so are most beneficial in non-obese patients
- ✓ They are also used in an obese patient who are unable to tolerate Metformin (due to contraindication or adverse effects) or have poor glycaemic control despite Metformin treatment
- ✓ Shorter acting agents (e.g. tolbutamide, gliclazide) are preferred in the elderly patient (hypoglycemia less likely) and both can used in mild to moderate renal impairment Insulin Formulation

#### Formulation Insulin Lispro, Aspart Rapid-acting Regular Short-acting NPH, lente

Intermediate-acting Glargine, ultralente Long-acting

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## **Gastrointestinal Tract (GIT)**

### **Anti-Emetics DOC**

- Mountain sickness------- Acetazolamide
- Motion sickness-----Scopolamine
- Morning sickness------Pyridoxine
- Chemotherapy-induced vomiting-----Ondansetron (MOA----5-HT3 antagonist)

### (1) Metoclopramide

- ✓ It is Centrally acting antiemetic
- It has the highest bioavailability
- ✓ Increase lower esophageal tone and speed up gastric emptying
- ✓ This is not acylated
- ✓ It is DOC in DM for Gastroparesis

### Antacid

- Aluminum hydroxide -----Cause-----Constipation
- Magnesium hydroxide ------Cause-----Diarrhea
- Ispaghoal husk is ------Bulk-forming laxative

### (1) Cimetidine:

- Cimetidine has steroid-like structure
- These are rapidly absorbed from the intestine, these undergo first pass effect
- Half-life is 1.1 to 4 hours
- Cause hepatic enzyme inhibition
- Ranitidine is different from cimetidine because of less CNS toxicity
- Sucralfate decrease absorption of cimetidine
- Antacid reduce the absorption of all H2 blocker

### Sucralfate:

- This complex of aluminum hydroxide and sulfated sucrose bind positively to positively charged groups in the protein of both normal and necrotic mucosa.
- By forming complex gel with epithelial cells, Sucralfate creates a physical barrier that protects the ulcer from pepsin and acid allowing, the ulcer to heal
- Because it requires an acidic pH for activation, Sucralfate should not be administrated with PPIs, H2 antagonist or antacids
- Sucralfate is well-tolerated, but it can interfere with the absorption of other drugs by binding with them.
- This agent does not prevent NSAID-induced ulcer, and does not heal gastric ulcers
- Hyoscine butylbromide, also known as scopolamine butylbromide and sold under the brand name Buscopan among others, is a medication used to treat crampy abdominal pain, esophageal spasms, renal colic, Billary colic and bladder spasms.

### Traveler's diarrhea treatment----DOC

- Bismuth subsalicylate----------Ist choice
- Loperamide-----2<sup>nd</sup> choice
- Ciprofloxacin > norfloxacin----3<sup>rd</sup> choice
- DOC in Fluoroquinolones resistant----azithromycin

### **Antibiotics**

Anti-Bacterial	MOA	
Aminoglycosides	Protein synthesis inhibitors	
Fluoroquinolones	DNA gyrase inhibitors	
Macrolide	Protein synthesis inhibitors	
Sulphonamides	Anti-folate antibiotics	
Cephalosporins	Cell wall synthesis inhibitors	
Ketoconazole	Inhibitor of steroid synthesis	
Vancomycin	Inhibitor of peptidoglycan biosynthesis o bacterial cell wall	
Metronidazole	It inhibits nucleic acid synthesis by disrupting the DNA of microbial cells	
Tetracycline	Tetracycline act by binding to the 30S subunit of the ribosome at the A-site thereby inhibiting protein biosynthesis and killing the bacteria.	

### Ciprofloxacin Indications

- · Pulmonary anthrax
- · Renal failure with a chest infection
- . D.M with pseudomonas infection
- . Enteric fever

### Antifungal

Systemic fungal infection--Amphotericin B (DOC for Cryptococcus neoformans)

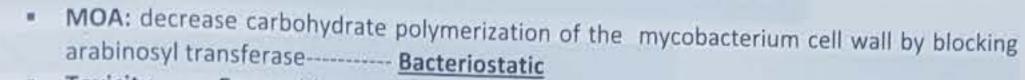
Penicillin

Amphotericin toxicity can be lower by using a liposomal delivery system

### DOC for:

- ✓ Gas gangrenes, if not in option then click Clindamycin
- ✓ Neisseria gonorrhoeae
- ✓ Infective Endocarditis, if allergic to penicillin than vancomycin (which need serum concentration monitoring) and Gentamycin are the drugs of choice
- ✓ Single-injection of Benzathine penicillin for streptococcus Pharyngitis
- Pronounced penicillin anaphylaxis----generalized skin rash
- Treatment of allergic anaphylaxis is---I/M adrenalin/epinephrine
- Benzathine penicillin has the longest duration of action
- Excretion of penicillin is inhibited by Probenecid
- Clavulanic acid with penicillin is used to inhibit Beta-lactamase
- Vancomycin is the drug of choice for infection caused by MRSA and MRSE. New drug with different mechanisms of action such as linezolid and daptomycin have been developed for vancomycin-resistant microbes Page | 584

### ( Ethambutol



Anti-Mycobacterial Drugs

Toxicity-----Eye problem-----optic neuropathy (red-green color blindness)

- Rifampin:
  - MOA: inhibit DNA-dependent RNA polymerase-----Bactericidal
  - Adverse effects:
    - ✓ Minor Hepatotoxicity and drug interaction, lead to nephrotic syndrome
    - Red/orange body fluids (urine, tears, saliva etc)
    - √ Thrombocytopenia
  - Most potent ATT and highly protein bounded
  - On discontinuation, patient can develop withdrawal symptoms
  - Reaches the CSF in meningeal inflammation
- (INH):
  - MOA: inhibit mycolic acid synthesis, for Bacilli in stationary phase----Bacteriostatic, for bacilli in rapidly dividing cell------Bactericidal
  - Isoniazid (a prodrug) is activated by mycobacterial Catalase -peroxidase
  - Metabolism occurs by the liver N-acetyltransferases (acetylation)
  - No need of dose adjustment in CKD patient
  - Toxicity:
    - ✓ Isoniazid induced hepatitis most common major side effect
    - **Drug induce SLE**
    - Peripheral neuropathy
    - Sideroblastic anemia
    - CNS toxicity -memory loss psychosis, seizure
    - ✓ Pyridoxine (vitamin-B6) can prevent neurotoxicity, lupus
  - Clinical use: the only agent used as solo prophylaxis against TB
  - Mnemonic: INH:-----Injure Neurons and Hepatocyte

### Pyrazinamide:

- It is an analogue of nicotinamide. It is active at acidic Ph
- Bactericidal
- Can kill persisters i.e. semi-dormant mycobacterial within the cell lysosome as well as in macrophage after phagocytosis because Ph of phagolysosome is low
- It can cross the BBB in inflamed Meninges
- Toxicity: Hyperuricemia (Podagra), Hepatotoxicity

### Streptomycin:

- First antibiotic effective in the treatment of tuberculosis
- Used when an injectable drug is needed or desired principally in individuals with a severe, possibly life-threatening form of Tb
- Streptomycin, Kanamycin, amikacin are around 80% excreted/eliminated unchanged in the urine without having undergone significant metabolism
- Side effects: 8th nerve damage, Nephrotoxicity
- Contraindicated in pregnancy

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Pharmacology

## Central Nervous System (CNS)

- The Daily dose of lithium should be started from------400mg
- Lithium is a mood stabilizer
- Narrow therapeutic index
- Excretion depend on renal excretion
- · Thiazide diuretic increases the toxicity of lithium
- Lithium may take up to 10-14 days to exert an effect
- . The Dose is adjusted to achieve the largest serum lithium concentration of 0.8-1 mmol/L
- Antimanic clinical effects of lithium occur in 5-7 days

### ( Side effects:

- ✓ Therapeutic dose cause——Fine tremor
- ✓ Toxic does cause------Coarse tremor
- ✓ Diabetic insipidus
- ✓ Leukocytosis, hypothyroidism
- √ Teratogenic
- ✓ Most common congenital anomaly is cardiac malformation.
- ✓ Symptoms depend on serum lithium level

### Diazepam

- Use as anxiolytic drug
- Relax skeletal muscle by acting on interneuron.
- Active metabolites of diazepam is Oxazepam
- Note: Liver metabolites of Benzodiazepines are also active compound, except oxazepam,
   temazepam and lorazepam so these can be given with liver compensation
- Side effects:
  - ✓ Most common adverse effect of diazepam if use during labour is fetal heart variability
  - √ I/V use cause Thrombophlebitis in 60% of cases
  - ✓ Sedation is common in diazepam and chlorpromazine

### Enilopey

### **Epilepsy Drugs**

### (2) Ethosuximide:

Chapter 25

- MOA: it decreases Ca<sup>++</sup> current of T-type
- Use for seizure, 3 spikes per second
- DOC for absence seizure

### (£) Lorazepam

- DOC for status epileptics
- Lorazepam is twice as potent as Midazolam
- Diazepam is the second line for status epileptics

### (2) Phenytoin:

- It therapeutic concentration, it blocks the Na<sup>+</sup> channel
- At higher concentration, it decreases GABA uptake and increases the density of GABA receptors
- It inhibits Monoamine oxidase inhibitors (MAOIs)
- It is 90% protein bounded
- Contraindications:
  - ✓ Febrile convulsion
  - ✓ Absence seizure
  - ✓ Liver disease
- Side effects: Frog-Pee
  - ✓ Folate deficiency, predisposing patient to Megaloblastic anemia
  - ✓ Rashes
  - ✓ Osteomalacia
  - ✓ Gum hypertrophy
  - √ Polyneuropathy

### Midazolam

- Midazolam, with its rapid onset and relatively <u>ultra-short duration of action</u>, has proven to be a useful premedication to decrease preoperative anxiety.
- Choice of drug for out-patient surgery and Paedraitic premedication
- Amnesic effects are more potent than sedative effects
- Hazardous in Hypovolemic patient

### CARDIOVASCULAR SYSTEM

**Drug Classification** 

Drug for decreasing preload:

✓ Diuretic and organic nitrates

Drug for decreasing after load:

✓ Hydralazine and minoxidil

Drug for decreasing of both preload and after load:

✓ Captopril, Enalapril, lisinopril

Theophylline

Its Dose is decreases in infants because of decrease metabolism

It inhibits erythropoietin

Theophylline worsen angina

The Most common side effect is nausea and vomiting

MOA In asthma is phosphodiesterase inhibitors

Dopamine Dopamine

Use in Cardiogenic shock, having shortest half so need continuous IV supply

Doesn't cross BBB

Half-life -----2min

Steady-state----8 min

Bromocriptine is dopamine agonist (D2 receptors agonist)

Calcium Channel Blockers (CCBs)

These drugs block the calcium channels, causing inhibition of Ca<sup>++</sup> influx into the cardiac and smooth muscles cells

( Verapamil:

It is the prototype drug

Directly acting on SA node, cardiac-specific

Nimodipine:

Freely cross the BBB, selective for cerebral blood vessels

DOC in Subarachnoid hemorrhage

🖺 Diltiazem:

It dilates peripheral and coronary arteries

🖺 Nifedipine:

\* Reduce the peripheral vascular resistance by vasodilation

It causes palpitation and tachycardia more commonly

£ Amlodipine:

Mostly used because it does not weaken the myocardial muscles in left ventricular failure

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MOA:

Pharmacology

✓ Increase the vagal activity

✓ It inhibits the Na<sup>+</sup>, K<sup>+</sup> pump by inhibiting Na-K ATPase, decrease in Na pump cause increase Na inside——slowing of extrusion of Ca<sup>++</sup> out there is——spontaneous activity in CNS and smooth muscle contraction

Digoxin

✓ increase Ca<sup>++</sup>-----increase smooth muscle contraction

√ digoxin reduce the symptoms of cardiac failure

Contraindication:

✓ MI

✓ Heart Block

✓ Ventricular tachycardia

√ Kidney disease (kidney have to excrete 2/3 of it as such)

(5) Indication:

✓ Atrial Flutters (at atrial rate 200-350/min)

✓ Atrial fibrillation

✓ Use in the patient of heart failure with AFib

✓ The Major indication is cardiac failure

✓ Paroxysmal supraventricular tachycardia

✓ It does not lower mortality in CCF patient

The Predisposing factor of toxicity:

√ Hypokalemia

√ Hypomagnesaemia

√ Hypercalcemia

✓ Old age

✓ Hypothyroidism

Propranolol

This is the prototype drug

Block beta 1 receptor in heart to decrease cardiac output

Patient taking propranolol develops increased PR interval the cause is—drug-induced first-degree heart block

Thyrotoxicosis with Atrial Fibrillation (AFib)———DOC———Beta blocker

 Glucagon is used as an antidote for beta-blocker toxicity because glucagon has positive Inotropic and chronotropic effects by activating adenylate cyclase.

( Indication:

✓ Anxiety -----stage fright

✓ Prevention of migraine

✓ Portal hypertension

✓ MI, angina

Side effects of beta-blockers

✓ Heart block

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- Hypoglycemia (in insulin-dependent DM)
- Intermittent claudication
- Reynaud' phenomena
- Erectile dysfunction
- Airway obstruction in asthma
- √ Na<sup>+</sup> retention

### Esmolol

- · Esmolol is a cardioselective beta<sub>1</sub> receptor blocker with rapid onset, a very short duration of action, and no significant intrinsic Sympathomimetic or membrane-stabilizing activity at therapeutic dosages.
- \* Esmolol is short-acting because it can metabolize quickly into an inactive form
- · Esmolol is rapidly metabolized by hydrolysis of the ester linkage, chiefly by the esterases in the cytosol of red blood cells and not by plasma cholinesterase or red cell membrane Acetylcholinesterase.
- · Esmolol short duration of action is based on the ester-methyl side chain which allows for quick hydrolysis.
- Esmolol is considered a soft drug one that is rapidly metabolized to an inactive form.
- Not dependant on hepatic/renal function
- Esmolol has a rapid distribution half-life of about 2 minutes and an elimination half-life of about 9 minutes.
- . Commonly used in the anesthesia to treat intra-operative tachyarrhythmia or to blunt the adrenergic response caused by various stimuli such as intubation, surgical stimulation, and extubation.

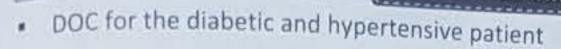
### Nitroglycerine

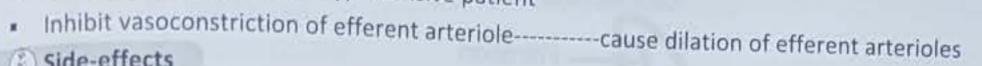
- MOA: Releases NO from smooth muscle, increase cGMP → relaxation, Vein > arteries
- It decreases Pre-load
- Undergoes extensive first-pass liver metabolism, that's why not given orally but given sublingually
- E Indication:
  - ✓ Angina pectoris
  - Acute decompensated CHF
  - Hypertensive crises
  - Per-operative hypertension in CV procedure
  - Pulmonary edema

### Chapter 25

### Pharmacology

### **ACE inhibitors**





### Side-effects

- ✓ Dry cough----Most common
- ✓ Decrease angiotensin II level and Aldosterone level
- ✓ Prevent Breakdown of bradykinin which is a potent vasodilator and thus Increase bradykinin level
- √ Hypotension
- ✓ Renal failure
- Angioedema (Enalapril)-----Enalapril is a prodrug
- √ Hyperkalemia
- ✓ Cause renal stenosis in infants

#### Diuretics

### ( Thiazide diuretic:

- MOA: Mainly acts on distal convoluted tubules inhibiting NaCl Co-transporter
- Decrease ca excretion
- Hydrochlorothiazide can be used to treat calcium-containing kidney stone because it decreases the amount of calcium excreted by the kidney in the urine and thus decreases the amount of calcium in urine to form stones
- Side effects:

Most widely recognized, the first adverse effect of thiazide diuretic is hypokalemia

✓ Metabolic alkalosis, Hypercalcemia, Hyperuricemia, hyperglycemia, Hyponatremia

### (A) Loop diuretic:

- Furosemide is the prototype drugs
- MOA: inhibit Na<sup>+</sup>, K<sup>+</sup>, 2Cl<sup>-</sup> cotransport system of the thick ascending loop of Henle
- Calcium looser, that's why used in Hypercalcemia
- Use in edematous states like CHF, cirrhosis, nephrotic syndrome and pulmonary edema
- Side effect:
  - ✓ Ototoxicity, hypokalemia, Gout, interstitial nephritis, hypocalcemia
  - ✓ All diuretic cause hypokalemia, Hyponatremia and hypotension except K sparing diuretic (Amiloride)
- ( Acetazolamide: (Sulfonamide derivatives), trade name Diamox
  - Cause H<sup>+</sup> reabsorption and K<sup>+</sup> and Na loss that why cause metabolic acidosis
  - Need zinc for its action
  - Indication:
    - ✓ Metabolic alkalosis
    - ✓ Use for mountain sickness
    - ✓ Aspirin/Phenobarbitone Poisoning—urine becomes alkaline for flushing out acidic drugs
    - ✓ Glaucoma

Urine

Excretion

### Chapter 25

### Pharmacology

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### Adverse effects:

- ✓ Skin rashes, Visual defects
- ✓ Hot flushes
- √ Hypercalcemia
- ✓ Endometrial cancer
- √ Vaginal bleeding
- ✓ Thromboembolism

### Cisplatin:

### Adverse effects:

- ✓ Severe nausea and vomiting up to 5 days after administration
- ✓ Nephrotoxicity-------Usually the dose-limiting toxicity
- ✓ Ototoxicity
  ——High-frequency loss, tinnitus
- ✓ Neurotoxicity------Paraesthesia, loss of proprioception

### Cyclosporine:

- MOA: Inhibit T-cell activation, it Decreases the level of IL-2, the primary chemical stimulus for increasing the number of T-lymphocyte
- Suppress only cellular immunity with no effect on Humoral immunity

#### Adverse effects:

- ✓ Hirsutism
- ✓ Gingival hyperplasia
- √ Hypertension
- √ Hyperkalemia
- ✓ Nephrotoxic without causing bone marrow suppression

### Methotrexate:

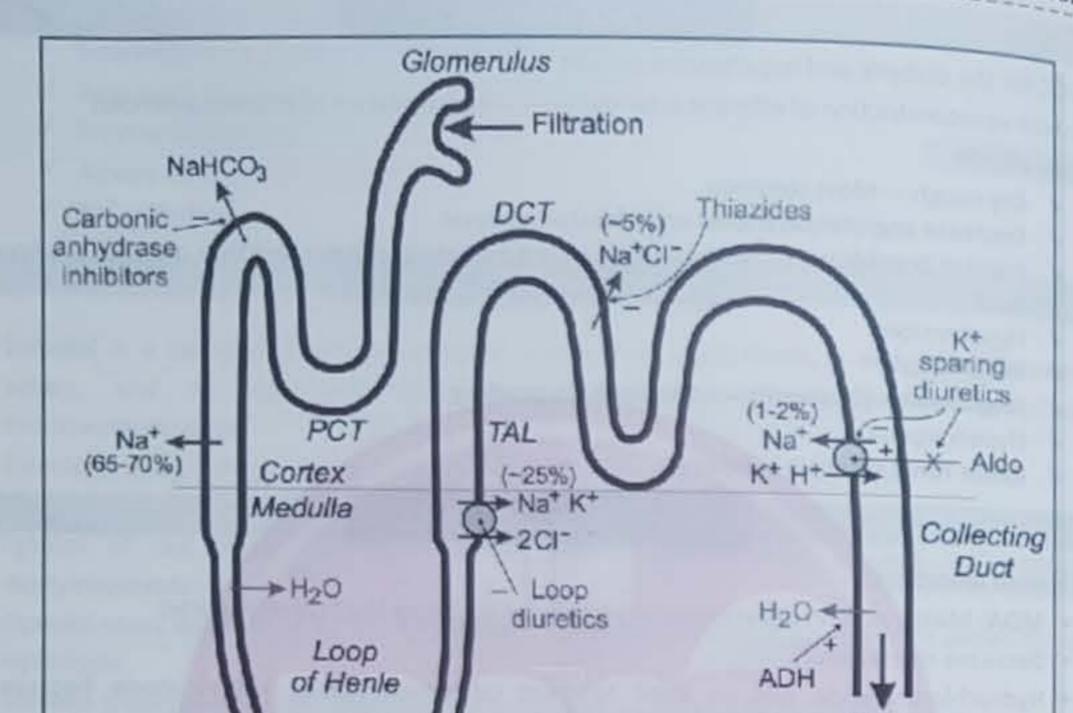
- It is the best initial DMARD
- It is Supplemented with folate

### Side effects:

- ✓ Pulmonary fibrosis
- √ Hepatotoxicity
- Bone marrow suppression
- Alopecia
- ✓ Mouth ulcer

## Naseem Sherzad High-Yield Points

- Tamoxifen is an estrogen receptor AGONIST in the uterus.
- Raloxifene is an estrogen receptor ANTAGONIST in the uterus.
- Tamoxifen for premenopausal women with breast cancer
- \* Aromatase inhibitors (Anastrozole) for postmenopausal women with breast
- Trastuzumab is a monoclonal antibody against HER2/neu and is indicated for patients with breast cancer that overexpress HER2/neu





## Cyclophosphamide:

- Side effects:
  - ✓ Alopecia
  - Myelosuppression
  - Hemorrhagic cystitis leading to bladder fibrosis and sterility

**Cancer Chemotherapy** 

### Bleomycin:

- It is highly concentrated in the skin and lungs but can't pass to the CSF
- Side effects:
  - ✓ Alopecia, Mucositis, blisters formation
  - ✓ Hyperkeratosis and hyperpigmentation
  - Pneumonitis and pulmonary fibrosis (Bleomycin lung)

### Tamoxifen:

- It is an estrogen antagonist
- Indication: estrogen dependant Ca breast

Chapter 25

Pharmacology

)		Pharmacology
Drugs Of Ch	oice	
D	anazol	
In	j Terlipressin>>>> inj C	Octreotide

Endometriosis-----

GI bleeding with CLD----

Acute/severe attack of ulcerative colitis-----I/V corticosteroid

Mast cell stabilization-----Sodium cromoglycate

\* The drug of choice for treating all species of Schistosoma and Taenia infection is-----Praziquantel

Invasive intestinal amoebiasis------Metronidazole/Tinidazole

Analgesic effect of antidepressant start at-----2 weeks and anti-depressant effects 3-4weeks

Malaria in pregnancy-----Chloroquine

Anaphylactic shock-------- Adrenaline

KALA-AZAR-----Liposomal amphotericin-B

Alcohol poisoning----- Fomepizole

Acute migraine------Sumatriptan

Acute gout-----NSAIDs

Cyanide poisoning------- Amyl nitrite

Acute digitalis toxicity------DIGIBIND

Paracetamol poisoning------- Acetyl Cysteine

Obsessive-compulsive disorder (OCD)-----Fluoxetine

Acute bronchial asthma-----Salbutamol

-Deferoxamine Iron poisoning-

-Phentolamine Cheese reaction---

Multiple myeloma	Melph:
Whooping cough or	pertussis

nalan

-----Erythromycin

Kawasaki disease-----IV Ig

Trigeminal neuralgia------Carbamazepine

Drug used to reduce triglyceride------Gemifibrazole

Most appropriate thrombolytic agent for coronary thrombosis------Streptokinase

Diabetic diarrhea-----Clonidine

Flumazenil duration of action------30-60min

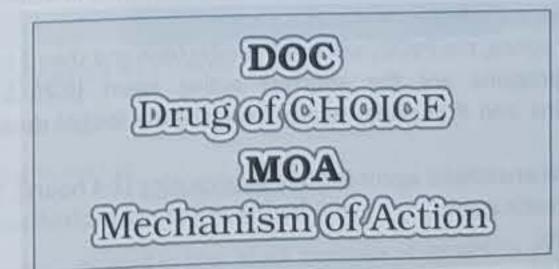
Cobalt half-life-----5 year

 Captopril is a potent and specific inhibitor of peptidyl - dipeptidase A. it blocks the conversion of angiotensin I to angiotensin II. The MOA of Captopril is as an angiotensin-converting enzyme inhibitors

Acetaminophen is metabolized by------Glucuronidation

Tramadol MOA: -----acts by binding to μ-Opioids receptors on neurons.

Cabergoline MOA------D2 agonist (more potent and more D2 selective)



**Ester Group** 

Metabolized in plasma

Cause allergic reaction

Anesthesia

To be in love is merely to in a state of perceptual anesthesia

### Local Anesthetic

- Mode of action of local anesthetics:
  - Decreasing the rate of depolarization
  - ✓ Prolonging the rate of Repolarization
  - Blocked of the sodium channel, Decrease in sodium conductance, No action potential
  - Failure to achieve the threshold potential level
- All local anesthetic possess some degree of vasoactivity, most producing some level of vasodilation
- Ester local anesthetic are potent vasodilating drugs
- Cocaine is the only local anesthetic that intrinsically causes vasoconstriction by blocking norepinephrine uptake
- All local anesthetic cross the blood-brain barrier
- All local anesthetic cross the placenta and enter the bloodstream of the developing fetus
- Onset and duration of local anesthetic depends on the PH of the tissue and lipid solubility
- All local anesthetics have the ability to cause sedation
- At high levels, local anesthetics will produce tonic-clonic convulsion
- Pre-convulsive signs and symptoms: numbness of the tongue and circumoral regions, shivering, slurred speech, muscular twitching
- The CNS is more sensitive to the effects of local anesthetics than the cardiac system and will generally manifest sign/symptoms of toxicity first
- A side effect unique to Prilocaine is methemoglobinemia at doses of at least 600mg
- Generally speaking, after a given injection with the same amount of local anesthetic, serum levels are highest following intercostal block followed by epidural block/caudal block. Absorption of local anesthetics---most to least----(intravenous, intercostal, caudal epidural, lumbar epidural)
- The abuse ability is greatest with cocaine. Ether should be avoided in diabetics
- The first anesthetic that was used in dentistry is cocaine
- During first minute of apnea, the PaCO2 will rise 6 mmHg/min and then 3 to 4 mm Hg each minute
- Procaine and Chloroprocaine are the shortest acting agent (0.25-.5 hours), followed by Lidocaine, Mepivacaine and Prilocaine, which have slightly longer duration of action (0.5-1.5 hour)
- The longer-acting local anesthetic agent include <u>Bupivacaine</u> (2-4 hours), Tetracaine (2-3 hours)
- Dosage of local anesthetic agent:
  - √ 0.5% = 5mg/ml
  - √ 0.1% = 10mg/ml √ 2.0% = 20mg/ml

¥	Prilocaine is metabolized in the liver and lungs		Ester is used only in patients with cirrhosis
	If the local anesthetic has two "I" in its name; it's an amide	•	Has one "I" in its name
	Lidocaine	*	Cocaine
	Mepivacaine		Procaine
	Bupivacaine		Chloroprocaine
*	Etidocaine		Tetracaine
	Pr <u>i</u> loca <u>i</u> ne		The second secon

### Lidocaine

Also known as Xylocaine

Ropivacaine

- MOA: inhibit the influx of Nat
- First effect C-fiber
- Preferred local anesthetics for local infiltration

**Amide Group** 

Primary site of metabolism of amide

local anesthetic is liver

- Use in arrhythmia because it inhibits the generation of the new impulse
- Moderate acting LA
- Sign of increase sensitivity is mild syncope
- Maximum safe dose= 4.5 mg/kg, maximum safe dose for 70kg person is 200mg
- 2% Lidocaine = 200mg/10ml or 20mg/ml
- Clinical signs of CNS toxicity: Lightheadedness, tinnitus, perioral numbness, seizure, obtundation and coma

### Bupivacaine

- MOA----block voltage-gated Na channel
- Best in chest injury and ribs fracture
- Side effect---ringing in the ear
- Toxicity-----Cardiac-toxicity or cardiac arrhythmia
- Bupivacaine is contraindicated in bier block because of its ability to produce cardio toxicity if it reaches the systemic circulation. Bier block is prepared in COPD patient with collie's fracture

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- Maximum safe dose---150
- Available in 0.5% solution
- Procaine is only 6% protein-bound and has a very short duration of action, whereas Bupivacaine is 95% protein bound, Bupivacaine have a longer duration of action
- Ropivacaine:
  - ✓ Ropivacaine is similar to Bupivacaine in onset and duration.
  - it has better safety profile in regard to CV toxicity when compared to Bupivacaine
  - Prilocaine overdose causes methaemoglobinaemia while Bupivacaine overdose causes treatment resistant ventricular arrhythmia and cardiac arrest

### Ketamine

- MOA: Non-competitive antagonist of CNS N-methyl-D-Aspartate (NMDA) receptors
- It decreases the cerebral blood flow, cerebral oxygen consumption
- it stimulates central sympathetic outflow that's why increase the heart rate, cardiac output and arterial BP
- Cause bronchodilation by intrinsic catecholamine release
- Ketamine produce dissociative anesthesia and profound analgesia
- I/M given in cardiac surgery
- Ketamine produces hallucinations (both visual and auditory. This hallucination and emergence reactions can be prevented by giving benzodiazepines along with Ketamine
- The Ideal choice for field anesthesia ---- Preserve BP and respiratory reflexes
- Preferred in: Bronchial asthma and anaphylactic shock
- Contraindication:
  - ✓ It increases the intracranial pressure (ICP) that why contraindicated in increase ICP
  - Schizophrenia and psychosis
  - Porphyria and Ketamine hypersensitivity
  - ✓ Age < 3months (increase risk of respiratory complication)</p>
  - Uncontrolled epilepsy

### Nitrous oxide (NO<sub>2</sub>): Laughing gas

- · Good analgesic but weak anesthetic--opposite of halothane
- Cause dilation of coronary vessels
- Doesn't depress respiration
- It may cause injury to bone marrow and can cause Megaloblastic anemia due to interference with Vitamin B12
- The Dose of nitrous oxide in 8 hours is 25ppm
- Histamine releasing: ATM
  - Atracurium
  - Tramadol
  - Morphine

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### Chapter 26

### Anesthesia

### Succinylcholine

### @ MOA:

- Physically resemble acetylcholine
- Act as acetylcholine receptor agonists
- Not metabolized at Neuromuscular Junction (NMJ)
- Metabolized by Pseudocholinesterase in plasma
- Depolarizing action persist > acetylcholine
- Continuous end-plate depolarization causes muscle relaxation

### Side effects

- ✓ Low blood pressure
- Cause fasciculation after muscle relaxation
- ✓ Salivary gland enlargement
- ✓ Succinylcholine half-life increase which leads to Succinylcholine toxicity in those having deficiency of enzyme Pseudocholinesterase
- ✓ Respiratory depression
- ✓ Malignant hyperthermia
- ✓ Post-operative muscle pain
- ✓ Cardiac arrest
- √ Jaw rigidity

### Propofol

- Most common intravenous agent
- Can be used as a continuous infusion
- Absolutely contraindicated in hypersensitivity
- It doesn't cause post-anesthetic nausea and vomiting
- It can be used both for induction and maintenance of anesthesia

- It is highly lipid-soluble ultra-short acting anesthetic
- It decreases the cerebral blood flow, cerebral metabolism and cerebral oxygen utilization----so desirable in cerebral swelling

Thiopental

- Increase venous capacitance and decrease CO, SV and decrease atrial pressure
- It may precipitate porphyric crises in the susceptible patient
- It is respiratory depressant and irritant for respiratory passage

### Paracervical Block

- Lignocaine without adrenaline is the most preferred drugs
- Give in the first stage of labor before the cervix is dilated 8cm at the base of the broad ligament
- The Pudendal nerve is not blocked, block Paracervical ganglion
- Fetal bradycardia is the worst complication

### Isoflurane

- Desflurane provides very rapid onset and recovery due to low blood availability
- This makes it a popular anesthetic agent for out-patient procedures
- However it has low volatility, requiring administration via a special heated vaporizer
- Like Isoflurane, it decreases vascular resistance and perfuses all major tissues very well
- It is relatively expensive and thus used rarely . for maintenance during extended anesthesia

- This agent undergoes little metabolism and is, therefore, not toxic to the liver or kidney
- Isoflurane does not induce cardiac arrhythmia or sensitize the heart to catecholamines.
- However like other halogenated gases, produces dose-dependent hypotension
- With higher blood solubility then Desflurane and sevoflurane, Isoflurane is typically used only when cost is a factor
- Isoflurane is the most potent coronary vasodilator

Sevoflurane

### Halothane

- This is a prototype inhalational anesthetic
- MOA: increase threshold of firing, decrease the rate of action potential due to decrease Na influx
- Doses not given in close circulation
- Halothane has a synergistic effect with calcium channel blocker (Nifedipine) and can cause refractory hypotension if given both at one time
- It is a potent anesthetic but weak analgesic, so co-administered with NO.
- This inhalation agent cause increase In cerebral blood flow
- Hepatic arterial blood flow decreased by halothane
- The Partial pressure of halothane: 243
- Side effects:
  - ✓ Malignant hyperthermia
  - particularly Arrhythmogenic in hypercapnia and Bradycardia

- Has a pleasant order that doesn't irritate airways
- Induction agent of choice in children
- It is an ideal bronchodilator
- Can be safely used in neurosurgery and coronary artery surgery
- Can be safely used in patient at risk of myocardial ischemia

### Airway irritability

- Desflurane-----Most irritant
- Desflurane/Isoflurane---irritant
- Halothane/sevoflurane---non-irritant-Thus preferred for inhalational induction
- All volatile anesthetic----potent bronchodilator
- potent Halothane----most followed by Isoflurane and sevoflurane

Chapter 26

Anesthesia

### Epidural (Extradural) anesthesia



- Deposition of local anesthesia in Extradural space
- Needles enter the spinal cord but does not penetrate the Meninges
- Inject between ligamentum flavum and dura matter i.e. without puncture of the dura mater
- It is ideal for post-operative pain, but does not produce adequate analgesia for surgical intervention
- Epidural anesthesia is given with 1:20000 epinephrine to increase its duration
- Urinary retention is common, necessitating catheterization of the bladder
- Hypotension-----slow
- Headache----is not a probable complication

### Spinal Anesthesia



- Inject into subarachnoid space, puncture of the dura matter occur
- . It is usually limited to surgeries below the segmental level of T10, because if it ascends too high, severe hypotension and ventilatory failure may occur
- Hypotension-----rapid, it causes autonomic sympathetic block, resulting in hypotension; so that patient should be preloaded with vasoconstrictor
- Headache------ Spinal headache is the most common complication (Occurs due to leakage of CSF) through the dura)

### Median approach:

- ✓ Most common, classic approach
- ✓ Through supraspinatus and infraspinatus ligament

### Paramedian approach:

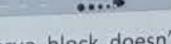
- ✓ Lateral approach, through ligamentum flavum
- ✓ Paramedian approach directly puncture ligamentum flavum

### Inferior Alveolar Nerve block: PCB



- Block lateral to Ptergomadibular raphe between superior Constrictor and Buccinators
- The Inferior alveolar nerve block is a nerve block technique that induces anesthesia in the angles of the mouth and face innervated by one of the inferior alveolar nerves which are paired on the left and right side.

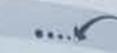




- Area of anesthesia: The area anesthetized is the skin of perineum, this nerve block doesn't, however abolish sensation from the anterior part of the perineum, which is innervated by ilioinguinal and Genitofemoral nerve
- Done through transvaginally or perineal approach
- The only landmark for transvaginally is the Ischial spine
- For the perineal procedure, Ischial tuberosity is the landmark
- Indication: During the second stage of labor, when presenting part of the fetus, usually the head,

is descending through the valve, Forcep delivery and episiotomy

### Stellate Ganglion Block



- A Stellate ganglion block is an injection of the local anesthetic in the sympathetic nerve tissue of the neck. These nerves are a part of the sympathetic nervous system.
- The nerves are located on either side of the voice box, in the neck

### Purpose of Stellate ganglion block:

- ✓ A Stellate ganglion block, blocks the sympathetic nerves that go to the arms, and, to some degree, the sympathetic nerves that go to the face.
- ✓ This may in turn reduce pain, swelling, color and sweating changes in the upper extremity. and may improve mobility. It is done as a part of the treatment of Reflex Sympathetic Dystrophy (RSD), Sympathetic Maintained Pain, Complex Regional Pain Syndrome and Herpes Zoster (shingles) involving an arm or the head and face.

### Hypothermia



- . During anesthesia, hypothermia may be defined as a core body temperature less than 36°C. This can cause physiological derangement in the operating theatre and in recovery, and may increase perioperative morbidity.
- Anesthesia should be induced only after core temperature is more than 36°C. IV fluids and blood products must be warmed to 37°C using fluid warming device. Use of FAWs is recommended to prevent and treat Perioperative hypothermia.

### Effects of Hypothermia:

- ✓ Increased morbidity; hypoxia. myocardial ischemia, arrhythmias and cerebral ischemia
- Decreased drug metabolism and prolonged duration of action
- Shivering
- Coagulopathy; the clotting cascade is enzymatic and platelet function is temperature dependent.
- ✓ Increased incidence of wound breakdown and infection

### Malignant hyperthermia:

- Transmitted genetically as an autosomal dominant disorder
- The most common triggering agents are volatile anesthetic gases, such as halothane, sevoflurane, desflurane, isoflurane, enflurane or the depolarizing muscle relaxants suxamethonium and decamethonium used primarily in general anesthesia. No IV anesthetic agent are known to trigger malignant hyperthermia
- ✓ Sign symptoms:
  - A rise in ETCo2 level is the earliest sign.
  - o In the absence of capnography, an elevated heart rate would most likely to be the first symptom.
  - o An increase in temperature is typically a late sign
- Dantrolene (MOA: inhibits Ryanodine receptor) prophylaxis can be given to high-risk patient of malignant hyperthermia.
- What receptor has been linked to malignant hyperthermia and where is this receptor found?
  - o The Ryanodine receptor, which is a major calcium release trigger located in the Sarcoplasmic reticulum.

# C H A P T E RBIOCHEMISTRY

### Vitamin Deficiencies in Different Conditions

Wat	er Soluble Vitamin-TRN	Fat Soluble Vitamin-KEDA		
B <sub>1</sub>	<u>T</u> hiamine	K		
B <sub>2</sub>	<u>R</u> iboflavin	E		
B <sub>3</sub>	<u>N</u> iacin	D		
B <sub>5</sub>	Pantothenic acid: CoA	А		
B <sub>6</sub>	Pyridoxine	<ul> <li>Absorption of fat-soluble vitamin depend on the gut (ileum) and</li> </ul>		
B <sub>7</sub>	Biotin	pancreas		
B <sub>9</sub>	Folate	<ul> <li>KEDA deficiency occurs in total pancreatectomy &amp; Cystic Fibrosis.</li> </ul>		
B <sub>12</sub>	Cobalamin	- All water-soluble vitamin washout from the body except B12 & folate		
.C 3	Ascorbic acid	(stored in liver)		

### Caloric Requirement

- Normal adult------40Kcal/kg/day, for 70kg 2800Kcal/day
- Adult with catabolism-----60Kcal/kg/day
- It is given as:
  - Protein------1gm/kg or 56gm per day or 10-35%
  - Carbohydrate-----2gm/kg or 130gm per day or 45-65%
  - Fats------0.5gm/kg or 44-78gm per day or 20-35%
  - Fiber-----28gm per day for male 25g/day for female

### . Caloric values:

- Protein-energy-----------4.1Kcal
- Carbohydrate-energy------4.1Kcal
- \* Fat-energy-----9.1kcal
- · Alcohol-----7 cal/gram

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Biochemistry

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### VITAMINS

"Small organic molecules present in diet, which are required in small amount"

### Thiamine—Vit-B1

- Thiamine deficiency causes Beri-Beri (peripheral neuropathy as a part of Beri-Beri syndrome) and lactic acidosis.
- Beri-Beri can cause high cardiac output failure
- Thiamine deficiency in developing country usually arise as a consequence of a diet based on polished Riceor parboiling, unhusked rice (paddy)
- In developed world thiamine deficiency is mainly encountered in chronic alcoholics.
- Thiamin is reduced/destroyed by heat labial thiaminases enzyme contained in milled rice, raw shellfish and freshwater fish.
- Increase carbohydrate consumption will increase the demand for thiamin.
- Rice is a good source of B group vitamins, especially Thiamine. Rice is devoid of vitamins A, D, iron and Vitamin C
- The Transketolase activity is measured in RBC's is an index of the thiamin status of an individuals
- The occurrence and manifestation of Wernicke-Korsakoff syndrome (WKS) which is seen in alcoholic patient and those with thiamin deficiency is due to genetic defect in the enzyme Transketolase

### Riboflavin---Vit- B2

- Riboflavin widely distributed in animal and vegetable foods.
- The Level is low in staple food but germination increases its content.
- Its deficiency cause glossitis, angular stomatitis, cheilosis and facial dyssebacea but only angular stomatitis can be used as an index of the state of nutrition of group of children.

### Niacin Vit-B3

- Niacin, which is synthesized in the limited amount in the body from Tryptophan.
- The deficiency of this vitamin cause Pellagra (Pellagra has been called the disease of Three Ds i-e Dermatitis, Diarrhea and Dementia).
- Maize contains Niacytin, a form of Niacin that the body is unable to utilize so it is more common in those who subsisted chiefly on Maize.
- Hartnup's disease: deficiency of neutral amino acid (tryptophan) transporter, result in pellagra

### Vitamin B5 (Pantothenate)

- Function: an essential component of CoA and fatty acid synthase
- Deficiency causes: dermatitis, enteritis, alopecia, adrenal insufficiency

### Chapter 27

### NASEEM SHERZAD FCPS - 1 HIGH-YIELD

Biochemistry

### Pyridoxine Vit-B6

- Converted to pyridoxal phosphate, a cofactor used in Transamination (e.g. ALT & AST) decarboxylation reaction, glycogen phosphorylase
- Isoniazid therapy is the most common cause of pyridoxine (vit b6) deficiency.
- Deficiency: convulsion, hyperirritability, peripheral neuropathy, Sideroblastic anemia due to impaired hemoglobin synthesis and iron excess

### Biotin Vit-B7

- The deficiency of biotin causes scaly dermatitis, alopecia and paraesthesia.
- Caused by antibiotic use or excessive ingestion of raw egg
- Biotin is co-enzyme in the synthesis of many fatty acids;
- It is a Cofactor for the carboxylation enzyme.

### Folate

- Celiac disease involves ---- Jejunum mostly----- So Folate deficiency.
- Pregnant lady with alcohol consumption the Most Common Vitamin Deficiency is Folate
- Pregnant woman-----Folate deficiency because of its more excretion due to increased GFR and Fetal tissue growth consumption.
- Tetrahydrofolates is single Carbon carrying fragment in an oxidative reaction
- FIGLU excretion test: used to asses folate deficiency
- Prevention of Neural tube defects (NTDs):
  - ✓ All NTDS occur between 17<sup>th</sup> and 30<sup>th</sup> day of conception
  - ✓ Adequate folate should be obtained in the first trimester of pregnancy
  - ✓ Folic acid supplementation reduce the risk of an NTDs in pregnancy

### Vitamin B<sub>12</sub> Deficiency

- Women strict vegetarian-B<sub>12</sub> deficiency in her and her baby if pregnant or none.
- Crohn's disease -----Involves Ileum so B<sub>12</sub> deficiency occur
- If vitamin B<sub>12</sub> deficiency coexists with folate deficiency, vitamin B<sub>12</sub> should be replaced first to prevent subacute combined degeneration of the spinal cord

### Vitamin C—Ascorbic acid

- Vitamin C is a cofactor in the conversion of dopamine to nor-epinephrine. It act as Antioxidant
- Vitamin C deficiency cause sCurvy due to Collagen synthesis defect
- Hemorrhage is the hallmark features of scurvy and can occur in any organ like Perifollicular hemorrhage, gum bleeding, conjunctival hemorrhage and bleeding into the myocardium and pericardial space
- Vitamin C is involved in the hydroxylation of proline to hydroxyproline.
- Hydroxyproline is found in abundant in collagen. Fisherman present with gum hypertrophy and bleeding, the cause is vitamin C deficiency
- Vitamin K and vitamin C both help in post-translational modification

### Vitamin K

- Vitamin K<sub>1</sub> is found chiefly in leafy green vegetables
- Newborn----due to sterile gut, because the most common source of Vitamin K is gut bacteria
- Hospitalized patient------Vitamin K>>>Biotin, Because of antibiotics use that kills gut bacteria
- Vitamin K can be synthesized by gut bacteria
- Gamma carboxylation of factors 27910, Vit-k take part in the formation of the clotting factors

- Function of vitamin-E
  - ✓ Act as anti-oxidant, protecting Vit-A, Vit -C, red blood cell and fatty acid from destruction

Vitamin E

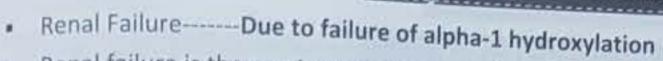
- ✓ Help in prevention of heart disease and cancer. Have some anti-aging effects
- ✓ It is the least toxic of all the fat-soluble vitamin Long term Vit-E intake increase the risk of hemorrhagic stroke
- ✓ Patient on Hyperbaric oxygen, should be given Vit-E to prevent lung injury induced by hyperbaric oxygen therapy
- ✓ Stop Vit-E intake 2 weeks before surgery because it may increase the risk of bleeding during surgery
- ✓ Anti-sterility vitamin, also used in the treatment of hypertrophic scar
- Symptoms of deficiency:
  - Cause Hemolytic anemia in children. Increased risk of cardiovascular disease
  - Neurological symptoms (impaired coordination and muscle relaxation)
  - impaired balance, abnormal sensation, muscle weakness and vision problem due to damage to the retina—retinitis Pigmentosa

### Vitamin A (RETINOL)

- Essential for normal differentiation of epithelial cell into specialized tissue
- Found in the liver and green leafy vegetables
- Liquid Paraffin used as a laxative can reduce the absorption of vitamin-A
- Vitamin A prevents squamous cell carcinoma.
- Use for treatment of measles and AML- subtype m3
- The first clinical sign of vitamin A deficiency: Conjunctival xerosis
- The first clinical symptoms of vitamin A deficiency: Night blindness
- Vitamin A deficiency result In delayed wound healing, specifically epithelization
- Hypervitaminosis A-----clinical features
  - ✓ Scaly dermatitis
  - ✓ Teratogenic
  - Pseudotumor cerebri
  - Also affects fetal brain and eye development
  - Produce bone hypertrophy
  - Papilledema
  - Stupor

**Biochemistry** 

## Vitamin D Deficiency



- Renal failure is the most common cause of vit D deficiency
- Colostrum (Breast milk up to 4 days) ----- deficient in Vitamin D.
- Postmenopausal women-----deficient in vitamin D

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- Vitamin-D is associated with animal sources, liver cod oil is the richest source
- Vitamin-D absorb along with the fat of the diet. Vitamin-D is the most toxic of all the vitamin Vitamin-D appears in lymph as a component of Chylomicrons
- The overall function of Vitamin D3 is to maintain plasma Ca level
- The mechanism of action of Vitamin-D is typical of steroid hormones
- Vitamin D insufficiency is regarded as a serum 25-hydroxyvitamin D level between 21 and 29 nanograms/mL.
- Calcitonin may be used in the intoxication of Vitamin D (vitaminosis-D)
- Vitamin-D deficiency cause ophthalmopathy in Gravs disease
- For Treatment monitoring: We check serum 25 hydroxy-cholecalciferol

### Vitamin D Metabolism

- Vitamin D3, obtained from the isomerization of pre-vitamin D3 in the epidermal basal layers or intestinal absorption of natural and fortified foods and supplements, binds to vitamin D-binding protein (DBP) in the bloodstream, and is transported to the liver.
- The First hydroxylation occurs in the liver: 24 Hydroxylation
  - Vita-D3 and D2-----by----25-hydroxylase-----result-------25 hydroxy-cholecalciferol
- 2<sup>nd</sup> hydroxylation occurs in the kidney: 1-Alpha Hydroxylation
  - o 25 hydroxy- cholecalciferol-----by-----1-Alpha Hydroxylase---1,25-Dihydroxy-cholecalciferol
- 1,25-Dihydroxy- cholecalciferol is the active form of vitamin D which has different effect on various target tissue of the body
- The synthesis of 1,25(OH)2D3 from 25(OH)D3 is stimulated by parathyroid hormone (PTH) and suppressed by Ca2+, Phosphate and 1,25(OH)2D3 itself.
- At higher calcium concentration, when PTH suppressed, the 25, hydroxy cholecalciferol is converted to a different compound 24, 25 dihydroxy cholecalciferol-----that has almost no vitamin effects

THE TOTAL STREET

### Minerals

### Zinc and Alcohol

### Zinc:

- Zinc deficiency occurs in Parenteral nutrition
- Zinc is necessary for carbonic anhydrase
- Zinc is one of the metalloenzymes involved in lipid, carbohydrate and nucleic acid metabolism.
- Zinc deficiency cause:
  - Delayed wound healing
  - Hypogonadism
  - Decrease adult hair
  - Dysgeusia (distortion of the sense of taste)
  - ✓ Anosmia and May predispose to alcoholic cirrhosis

### Alcohol:

- Cause Folate deficiency
- Thiamine (vitamin B1) deficiency, which can lead to an alcoholic brain disease known as Wernicke-Korsakoff syndrome (WKS)
- Most common deficiency of Mg—metal

### Magnesium

- The highest amount found in bone and it is the 2<sup>nd</sup> abundant intracellular cation
- Severe Hypomagnesaemia (<6 mg/dL) can lead to hypocalcemia by inhibiting PTH secretion, mild hypomagnesemia cause Hypercalcemia
- Treatment of magnesium deficiency: Parenteral magnesium sulfate or magnesium chloride
- Hypermagnesemia:
  - ✓ Impair the release of acetylcholine and decrease motor end-plate sensitivity to acetylcholine in muscle
  - Decreased or Loss of deep tendon reflex is the earliest clinical indication of Hypermagnesemia
  - ✓ Nausea, vomiting and Weakness

### **Breast Milk and Cow Milk**



- It is a sufficient source of iron for first the 4-6 months in term infants.
- Breast milk is deficient of Vitamin C, K, D fluoride and Pantothenic acid
- Lactalbumin is the major protein in breast milk.
- Important to note that if a baby because of any reason is on goat milk they need to have folate supplementation because folate is deficient in goat milk
- Breast milk confers passive immunity

### Cow's milk:

 Caseinogens forms 90% of the protein of the cow milk; sodium is higher in cow milk, which can therefore be dangerous if given to a baby who is dehydrated from gastroenteritis.

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## **Calcium and Phosphate**

Biochemistry

### A Overview:

The vast majority (99%) of total-body calcium and phosphate are stored within the bones and only a fraction circulates within the extracellular fluid. This extracellular supply of calcium and phosphate can in different physiological forms which exhibit distinct physiological activities.

#### Extracellular calcium:

- Protein Bound: 40%
  - ✓ Roughly 40% of extracellular calcium is bound to plasma proteins such as albumin. Importantly, this protein-bound supply cannot diffuse through capillaries and remains within the vasculature.
- Chemically Bound: 10%
  - ✓ Roughly 10% of the extracellular calcium is complexed with anions such as phosphate and citrate. Although this chemically-bound supply of calcium can diffuse through capillaries it is not physiologically active.
- Free Calcium: 50%
  - Roughly half of the extracellular calcium is in its free ionized form as Catt. Ionized calcium is freely diffusible through the capillaries and is the only physiologically active form of the calcium. Thus, discussions of regulatory mechanisms of calcium concentration are in reality only referring to this free, ionized form of the atom.

### Extracellular Phosphate:

- Extracellular phosphate is present in inorganic form as either HPO<sub>4</sub><sup>2-</sup> or H<sub>2</sub>PO<sub>4</sub>.
- The differences between these two ionic forms of phosphate are physiologically negligible and biochemically difficult to distinguish; consequently, most discussions of extracellular phosphate will conflate these two pools as total phosphorous.

Hypercalcemia

### Cause of Hypercalcemia: Malignancy----most common cause

- Vit-D intoxication
- Granulomatous disease----e.g. Sarcoidosis
- Paget disease of bone
- ✓ Milk-alkali syndrome
- ✓ Thiazide diuretic

### Clinical features:

- ✓ Dehydration
- Constipation, confusion
- Polyuria and polydipsia
- ✓ Short QT-interval on ECG

### Treatment:

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- ✓ Hydration---high volume of normal saline----lst step
- Furosemide is given only AFTER hydration
- Calcitonin---if hydration and diuretic fails to control calcium levels
- ✓ Bisphosphonate

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### A Complications:

- ✓ Cause zinc deficiency
- ✓ Hyperglycemia is the most common complication and is directly related to PN dextrose contents, the patient glucose tolerance and the rate of TPN infusion
- Cause hypokalemia, hypophosphatemia, hypomagnesemia and volume overload
- Abnormalities of liver enzymes are common in patients receiving TPN
- ✓ The most common side effect of TPN is mouth sores, poor night vision, and skin changes.

### Contraindication:

- Cardiac failure
- Altered fat metabolism
- Cause hyperglycemia that's why contraindicated in uncontrolled DM
- Blood dyscrasias



### **Important Topics**



### Smoking:

- Smoking cause Vitamin C deficiency
- Not only does smoking decrease absorption of vitamin C, it also increases the body's requirements for vitamin C by 30 percent
- Smoking increase Elastase level
- In smoker lung injury most appropriate investigation is: Carboxyhemoglobin

### Antioxidants-----ACE

- Vitamin A
- Vitamin C
- Vitamin E

### Essential fatty acid

- Linoleic acid
- Linolenec acid

### A Homocystinuria and Homocystinemia

- Vit-B12 deficiency------Homocystinemia
- Vit-B6 deficiency -------Homocystinuria

### Enzyme:

- Enzyme are proteins that act as a biological catalyst
- They lower the activation energy of a specific chemical reaction n
- Lowering the activation energy has a profound effect on how rapidly the reaction completed

## **Essential AA and Non-Essential AA**



### Essential Amino Acids (AA)



Biochemistry

Essential amino acid can't be synthesized by the human body and must be obtained from the daily diet. Also known as indispensable amino acid

- · Leucine,
- Isoleucine,
- Lysine,
- Valine
- Methionine
- Phenylalanine
- Threonine
- Tryptophan: Serves as a precursor for the vitamin Niacin and serotonin
- Histidine

### Naseem Sherzad High-Yield Points

- \* Ketogenic amino acid: Leucine and lysine
- sulfur-containing amino acids: Cystine and Methionine
- . Acidic: Glutamic acid and aspartic acid
- ❖ Basic:
  - ✓ There are three amino acids that have basic side chains at neutral pH.
  - These are Arginine, lysine, and histidine.



### Non-essential AA



Non-essential amino acids can be synthesized by the human body. Also known as dispensable amino acid

- Alanine
- Arginine-----This is the source of nitrous oxide (NO)
- Asparagine and Aspartic acid
- Cysteine
- Glutamic acid
- Glutamine: it is a major fuel for the small intestine mucosa and other replicating cells such as lymphocytes, macrophages, fibroblasts and endothelial cells
- Proline
- Serine
- Tyrosine

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Kwashiorkor

Sign Which Is Always Present

The child is weak and wasted but has

Psychomotor changes e.g. apathy

Growth failure (wasting marked by

Edema is always present (potbelly).

some subcutaneous fat.

and irritability

Puffy, moon face

· Hair changes are present

edema)

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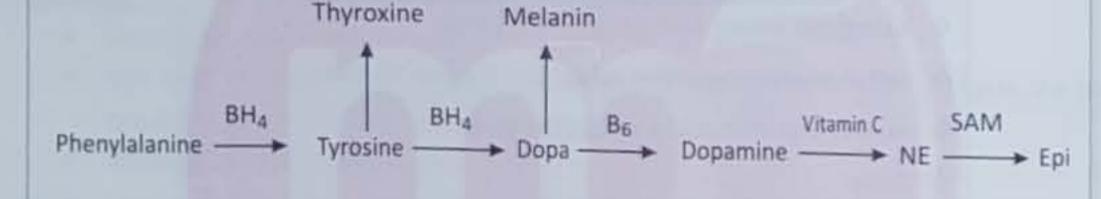
### Glycine

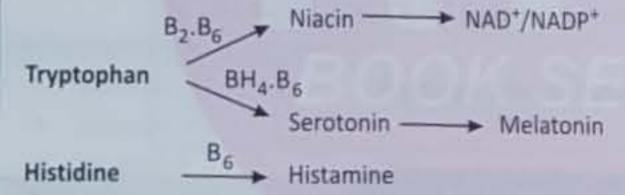
- Deficiency of Glycine can cause cell injury
- Smallest AA,
- This is the Inhibitory neurotransmitter in the spinal cord

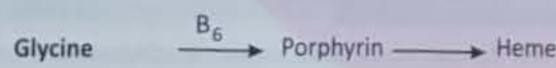
### Tyrosine derivatives

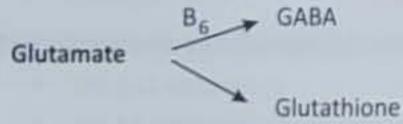
- T3 and T4
- · Epinephrine and nor-epinephrine
- Dopamine

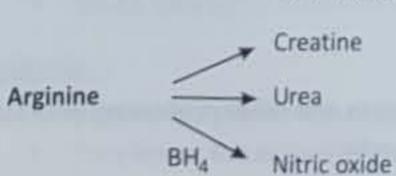
### Amino acid derivatives











BH<sub>4</sub> = tetrahydrobiopterin

### Carbohydrates

### Major dietary CHO are starch, sucrose and lactose

Difference between Marasmus and Kwashiorkor

0	Starch	Polysaccharide
---	--------	----------------

subcutaneous fat

· Hair are normal

- Sucrose-----Disaccharide
- Fructose-----monosaccharide
- Glycogen----------Animal Homopolysaccharide

Marasmus

Sign Which Is Always Present

Extreme growth failure and weight

below 60% of the expected weight

· Patient is usually alert and has a good ·

Face is wizened and shriveled like

Marked Muscle wasting and loss of

"little old man" or monkey face.

Edema is absent

appetite.

- Dextran——Polysaccharide, used in Hypovolemia to prevent further loss of water, used in patient with low BP
- Sorbitol is a <u>sugar alcohol</u> found in fruits and plants with diuretic, laxative and cathartic property. Unabsorbed sorbitol retains water in the large intestine through osmotic pressure thereby stimulating peristalsis of the intestine and exerting its diuretic, laxative and cathartic effect.
- The Human can easily tolerate the lack of Carbohydrate in the nutrition

### Vitamin which increases intake of following

- Thiamin increase intake of -----Carbohydrate
- Biotin increase intake of -----Lipid
- Riboflavin increase intake of ------Protein

NASEEM SHERZAD FCPS -1 HIGH-YIELD

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Biochemistry

## Naseem Sherzad High-Yield Points

*	Ire	on dei	mand	in p	oregn	ancy	/	800	mg

- \* Ca<sup>++</sup> requirement in pregnancy------------------1200mg
- Content of fat in male------15%
- The baseline protein requirement as calculated as--1g/kg/day
- Amount of energy produced by cereals-----350-450
- Number of bonds broken in protein synthesis-----Four
- High energy compound/molecule-----ATP
- High energy content————————Starch
- Dietary fiber contains-----Starch
- . Least amount of minerals are found in-----Tubers
- ATP needs------Magnesium
- Soup contains increase amount of-----Sodium
- Cholesterol enriched in------Egg yolk
- · Cereal contains the highest amount of-----Carbohydrate (CHO)
- The End-product of purine metabolism-------Uric acid
- Lipid soluble in-----Soap water
- Uncoupling of O<sub>2</sub> is done by-----Nor-epinephrine
- The Earliest definite sign of brain death is ------Absent brain stem reflex
- Hormones relation between weight & puberty——Leptin
- Pyruvate is an intermediate between------Glucose and acetyl co-A
- The End-product of glucose or carbohydrate breakdown————Pyruvate
- The exact releasing site of glucokinase is————————————————Cytoplasm of Hepatocyte
- Major energy reservoir in human is—————————————————————Adipose triglycerides
- Acetyl-CoA can be directly converted into fatty acid, cholesterol and ketone bodies
- \* Ketosis is normal metabolic process. When the body does not have enough glucose for energy, it mobilizes and burn stored fats instead
- \* Apple is rich in Phloretin 2-glucoside compound which is naturally polyphenol and has been demonstrated to exert anticancer activity
- · Negative Aspects of Junk Food: Lack of vitamins such as A and C, and minerals such as magnesium and calcium, encourage the development of deficiency diseases and osteoporosis, as well as dental caries due to higher sugar intake.
- Soybean oil is composed of approximately 16% saturated fatty acid, 24% mono-unsaturated acids and 60% unsaturated acid
- Dark green leafy vegetables are good sources of many vitamin that's why dietician advised green vegetable with vitamin
- \* Vitamin D and K: Helping to keep your heart and bones healthy. Separately K2, regulates normal blood clotting while D3 support a healthy immune system and support muscle function

**Low-Density Lipoprotein (LDL)** 

### Chylomicrons

### Contain Highest cholesterol

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- LDL transport cholesterol from the liver to the tissue
- \* Statins: Inhibits enzyme HMG-CoA reductase. Cause decrease cholesterol levels, increase synthesis of LDL receptor thus increase LDL clearance. Use for decreasing LDL level

### High-Density Lipoprotein (HDL)

- Contain Highest protein
- HDL transport cholesterol from periphery to the liver
- \* Negative coronary risk factor, heartprotective
- · Gemfibrozil: decrease plasma triglyceride levels and increase plasma HDL level

- . Chylomicrons are the largest and most TG-rich lipoproteins in the blood.
- Deliver dietary TGs to peripheral tissue
- Secreted by intestinal epithelial cell
- Absent during fasting, more in those who eat more burger and fries

### Very Low-Density Lipoprotein (VLDL)

- \* VLDL contain Highest triglyceride, Main component of VLDL: Cholesterol: 10%, Triglyceride: 70%
- Deliver hepatic TGs to peripheral tissue.
- Secreted by liver
- Hyperlipoproteinemia type-1 is due to deficiency of lipoprotein lipase deficiency

### ATP calculation in Glycolysis

### Aerobic

- Aerobic Glycolysis of glucose net ATP Gain: 08 ATP
- Aerobic Glycolysis of glycogen net ATP Gain: 09 ATP

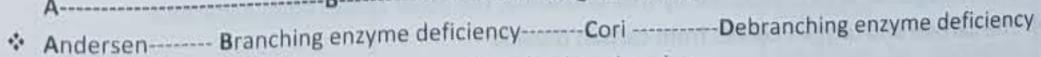
### Anaerobic

- Anaerobic Glycolysis of Glucose net ATP Gain: 02 ATP
- Anaerobic Glycolysis of Glycogen net ATP Gain: 03 ATP

### Rate limiting steps:

- Glycolysis (occur in the cytosol), the end product of aerobic Glycolysis: Pyruvate and end product of anaerobic Glycolysis is: lactate
- Rate limiting step of Glycolysis: Fructose-6-PO4 to fructose-1,6- bisphosphatase

### Glycogen And Lysosomal Storage Disease



- \* Mcardle disease------Muscle phosphorylase
- Von Gierke disease ------Glucose-6-phosphatase
- \* Tay Sachs disease -----TSH
- Niemann-Pick diseases -------Sphingomyelin -----NPS Most common clinical finding/symptom encountered after glycogen storage disease is
- Hepatomegaly and hypoglycemia

\*\*\*\*

- Nitrogen balance is a measure of nitrogen input minus nitrogen output
- Sources of nitrogen: Sources of nitrogen intake include meat, dairy, eggs, nuts and legumes,
   grain and cereals
- Loss of nitrogen: example of nitrogen loss include urine, feces, sweat, hair and skin
- Estimation of nitrogen: Blood urea nitrogen can be used in estimating nitrogen balance, as can the urea concentration in urine
- Nitrogen balance and protein metabolism: Nitrogen is a fundamental component of amino acid, which are molecular building blocks of protein. Therefore measuring <u>nitrogen input and loss can</u> be used to study protein metabolism
- Positive nitrogen balance: Positive nitrogen balance is associated with period of growth, hypothyroidism, tissue repairs and pregnancy. This means that intake of nitrogen into the body is greater than the loss of nitrogen from the body, so there is increase in the total body pool of protein. Positive nitrogen balance is associated with muscle gain
- Negative nitrogen balance: It is associated with <u>burns</u>, <u>serious tissue injury</u>, <u>fever</u>, <u>hyperthyroidism</u>, <u>wasting diseases</u>, and <u>during period of fasting</u>. A negative nitrogen balance can be used as part of clinical evaluation of malnutrition
- 1 g of nitrogen is equivalent to 6.25g protein

### Urea Cycle

- Also called as Krebs- henseleit cycle or ornithine cycle
- Account for 90% of nitrogen-containing component of urine
- It is an important source of Arginine
- The urea cycle occurs in the liver. First two reactions in mitochondria and rest in the cytosol
- The 2 nitrogen atoms of urea enter the urea cycle as NH<sub>3</sub> (produced mainly via glutamate dehydrogenase) and as the amino N of Aspartate
- One nitrogen of urea is supplied by free ammonia, the other comes from Aspartate
- The carbon and oxygen comes from carbon dioxide

### One carbon Transfer Reaction

Common reaction type, the involvement of one of three cofactors

- \* Biotin: one-carbon transfer of most oxidized state, CO2---imp
- \* Tetrahydrofolate: one-carbon transfer of intermediate oxidation states of methyl groups
- S-adenosylmethoinine: one-carbon transfer of most reduced state, CH3

---- Biochemistry

Rate-Determining Enzymes of Metabolic Process

Process	Enzyme	Regulators
Glycolysis	Phosphofructokinase-1	
Gluconeogenesis	Fructose-1, 6 bisphosphatase	
TCA cycle	Isocitrate synthase	Allosteric activation by: ADP Allosteric inhibition by: NADH
Glycogen synthesis	Glycogen synthase	Newton married at the
Glycogenolysis	Glycogen phosphorylase	Activated by: AMP, epinephrine, glucagon Inhibited by: insulin, ATP
HMP shunt	Glucose-6 phosphate dehydrogenase (G6PD)	
De novo pyrimidine synthesis	Carbamoyl phosphate synthetase II	
De novo purine synthesis	Glutamine-PRPP amidotransferase	
Urea cycle	Carbamoyl phosphate synthetase I	
Fatty acid synthesis	Acetyl-coA carboxylase	Activated by: insuling citrate Inhibited by: glucagon palmitoyl-CoA
Fatty acid oxidation	Carnitine acyltransferase I	
Ketogenesis	HMG-coA synthase	
Cholesterol synthesis	HMG-coA reductase	Activated by: insuling thyroxine Inhabited by: glucagon, cholesterol
Bile-acid synthesis	7 alpha-hydroxylase	
Heme synthesis	Aminolevulonate synthase	The state of the s

### Summary of Physiological response to starvation

- Glucose is the general metabolic fuel, and can be metabolized by any cell.
- . Glucose can be obtained directly from dietary sugars and by the breakdown of other carbohydrates. In the absence of dietary sugars and carbohydrates, glucose is obtained from the breakdown of stored glycogen. Glycogen is a readily-accessible storage form of glucose, stored in notable quantities in the liver and skeletal muscle.
- . When the glycogen reserve is depleted, glucose can be obtained from the breakdown of fats from adipose tissue. Fats are broken down into glycerol and free fatty acids, with the glycerol being turned into glucose in the liver via the gluconeogenesis pathway.
- . When even the glucose made from glycerol reserves start declining, the liver starts producing ketone bodies. Fatty acids can be used directly as an energy source by most tissues in the body. Hepatic
- . After the exhaustion of the glycogen reserve, and for the next 2-3 days, fatty acids are the principal metabolic fuel.
- . After several days of fasting, all cells in the body begin to break down protein. This releases amino acids into the bloodstream, which can be converted into glucose by the liver. Since much of our muscle mass is protein, this phenomenon is responsible for the wasting away of muscle mass seen in starvation. Gluconeogenesis from peripheral tissue lactate and Alanine, and from adipose tissue glycerol and proppionyl-CoA (from odd chain fatty acid----the only triglyceride components that contributes to Gluconeogenesis
- \* The ultimate cause of death is, in general, cardiac arrhythmia or cardiac arrest brought on by tissue degradation and electrolyte imbalances.
- In very obese persons, it has been shown that proteins can be depleted first and death from starvation is predicted to occur before fat reserves are used up.
- Postabsorptive state: also called the fasting state; the metabolic state occurring after digestion when food is no longer the body's source of energy and it must rely on stored glycogen. The source of metabolic fuel for liver during Postabsorptive state is glucose
- All the organs are atrophied and have subnormal weights at necropsy except the brain, which tends to maintain its weight.
- Starvation, and more precisely carbohydrate deprivation, appears to rapidly inhibit deiodination of T4 to T3 by type 1 iodothyronine deiodinase in the liver, thus inhibiting the generation of T3 and preventing metabolism of reverse T3 (rT3). Consequently, there is a drop in serum T3 and elevation of reverse T3. Since starvation induces a decrease in basal metabolic rate
- Glycogenolysis provide glucose during a short period of fasting, between meals and during sleep etc

## Effect of Heat and Cold

### Heat Cramp:

- Cramp means painful contraction of muscle so heat cramp means painful contraction of the voluntary muscle following vigorous exercise and profuse sweating in hot weather.
- Core body temperature remains normal
- The Result from loss of electrolyte (mainly extracellular sodium depletion) via sweating.
- Sodium loss (Hyponatremia) is responsible for cramping which will exacerbate by replacement of water only.
- The Symptom usually responds rapidly to rehydration by oral rehydration salt or intravenous saline.

### Heat Exhaustion:

- It is the most common hyperthermic syndrome.
- It happens with prolongs exertion in hot and humid weather, perfuse sweating and inadequate salt and water replacement.
- Core body temperature will be elevated
- Clinical feature: tachycardia, headache, fatigue, weakness and irritability etc.
- Treatment:
  - ✓ First step to Remove the patient from heat source,
  - ✓ Active evaporating cooling can be done by tepid spraying and fanning( strep-sprayfan)
  - Fluid losses are replaced with either oral rehydration mixtures or intravenous isotonic saline.
  - ✓ Note: untreated heat exhaustion maybe progress to heat-stroke.

### Heat-Stroke:

- A life-threatening condition
- Core body temperature rises above 40 centigrade
- Occur in high ambient temperature, high humidity and with exertion.
- There is generalized vasodilatation and peripheral pooling of blood.
- The patient's skin dry and feels very hot, and Sweating often absent due to loss of thermoregulatory mechanism.
- Clinical feature: Headache, nauseas, vomiting, coarse muscle tremor, confusion, aggression or loss of consciousness, hyperkalemia and tachycardia
- Treatment:
  - o Rapid cooling must be done using water spray, fanning, ice pack in axillae and groin.

### o Prevention:

- ✓ Protective devices: protective goggles shields and helmets are helpful
- ✓ Clothing: should be light, loose, and of light colors
- ✓ Working environment: temp and humidity should be controlled by proper
- ✓ Regulation of work: duration of exposures to the hot environment should be

### Heat Syncope:

- Syncope means a temporary loss of consciousness and posture, fainting or passing out
- In hot weather, syncope is occur due to peripheral vasodilatation, which causes temporary insufficient blood flow to the brain.
- This will cause a transient loss of consciousness and posture that will be referred to as heat syncope.
- Treatment is to bring the patient in shade with head down.



### **Cold Injury**

## Frostbite (freezing cold injury)

- This represents the direct freezing of body tissue and usually affects the extremities, particularly the finger, toes, ear and nose.
- The tissue may become anesthetized before freezing.
- Treatment:
  - ✓ Give oxygen and aspirin 300mg as soon as possible.
  - ✓ Frostbitten extremities should be rewarmed in warm water at 37-39 centigrade with antiseptic added.
  - ✓ Adequate analgesia is necessary, as rewarming is very painful.

## Trench or immersion foot (non-freezing cold injury)

- This result from prolonged exposure to cold, damp condition
- The limb (usually the foot) appears cold, ischemic and numb but there is no freezing of the tissue.
- Treatment: control by giving Amitripyline (50 mg nocte)

## CHAPTER

### SHOCK, BLOOD TRANSFUSION & TRANSPLANTATION

### Shock



- Decrease tissue or cellular oxygenation
- Shock gives rise to systemic hypoperfusion; it can be caused either by reduced cardiac output or by reduced effective circulating blood volume. The end results are hypotension, impaired tissue perfusion, and cellular hypoxia.
- Decreased mixed venous oxygen (MVO2) is the best indicator of tissue hypoxia
- There is metabolic acidosis in the progressive stage of shock due to increase lactate levels.
- Lactic acid accumulation indicates an adverse prognosis in shock
- MODS is the most common cause of death in shock
- Tachycardia is the first finding in all types of shock (Only in Neurogenic shock: Bradycardia)
- Successful fluid replacement indicated by increase in urine output
- Most important response in shock as a whole is CNS Ischemic response
- The key diagnostic sign of fluid overload (Hypervolemia) include weight gain and swelling

### Hypovolemic Shock

- It is the most common form of shock
- Hypovolemic shock results from loss of blood or plasma volume
- Massive blood loss is the most common cause, other causes included vomiting, diarrhea, dehydration, third space loss and Burn
- Number of red blood per unit volume of plasma is the last to return after Hypovolemic shock
- Baroreceptor reflex is important in case of Hypovolemic shock
- Hypothermia due to decreased perfusion and evaporation of sweat
- An alternative to the classical system is to divide the Hypovolemic shock into Covert compensated hypovolemia, overt-compensated hypovolemia and overt-decompensated hypovolemia. Covert-compensated hypovolemia is the most common, yet the least often diagnosed form of Hypovolemia. As a result, Covert -compensated hypovolemia is probably associated with the greatest morbidity

### Clinical features:

- ✓ Heart rate: Tachycardia
- ✓ Skin flushed and moist

cyanotic skin.

- ✓ Cool, clammy skin is due to vasoconstriction
- ✓ The patient presents with hypotension; a weak, rapid pulse; tachypnea; and cool, clammy,

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### **Neurogenic Shock**

- Occur due to Loss of vasomotor tone or loss of sympathetic nervous system tone, total peripheral resistance is mainly due to vasomotor tones
- Decrease CVP, Heart rate: Bradycardia
- Peripheral vasodilation and venous pooling and hypotension

#### Causes:

- ✓ Spinal anesthesia or deep general anesthesia
- Spinal cord injury above T6
- Vasomotor center depression (severe pain, drug, hypoglycemia)
- Reaction to fear or fight or hearing bad news

### **Naseem Sherzad High-Yield Points**

- Cardiogenic shock DOC: Dopamine
- Anaphylactic shock DOC: I/M Adrenaline/Epinephrine

### **Blood Transfusion (BT)**

- Cross-matching of blood is required to prevent transfusion reaction. Cross-matching of blood takes about 45 minutes in most laboratories
- Packed cells are stored in a SAG-M solution to increase the shelf life to 5 weeks at 2-6 °C
- Multiple or Repeated long term blood transfusion can cause Hemochromatosis, most commonly seen in Thalassemia patient
- If a patient needs multiple blood transfusion for surgery the ideally cross-match should be done after every bag
- In an anesthetized patient sign of transfusion reaction are oozing and hypotension

### **Hemoglobin level and Transfusion**

- Hb less than 6gm/dl, transfusion will benefit the patient
- 6-8 g/dl= transfusion unlikely to be benefits in the absence of bleeding or surgery
- >8gm/dl= no indication for blood transfusion

### Complication of Blood transfusion

- \* Hypothermia may lead to cardiac arrhythmia including fibrillation and asystole. For this reason, blood warming is necessary if the blood transfusion rate exceeds 50ml/min
- \* Hyperkalemia may occur in stored blood, potassium level increase by 1meq/L/day, not a problem unless a very huge amount of blood is given quickly

Massive transfusion	<ul> <li>Massive transfusion is defined as the replacement of total blood volume within a 24-hour period or about 5L in adult</li> <li>This can lead to Hypocalcemia; excess citrate can act on the patient plasma free ionized calcium and result in hypocalcemia</li> <li>Cause Hyperkalemia, hypokalemia and hypothermia</li> </ul>
Multiple transfusion	Hypocalcemia, Hyperkalemia and hypokalemia
Repeated transfusion	Iron overload (in patient with Thalassemia)

Reference: Bailey & Love's Short Practice of Surgery,

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#### Blood Blood Loss Loss Decreased Altered Blood Arterial Pressure Gases RAAS Catecholamine Vasopressin Activation Release Release Baroreceptor Chemoreceptor Reflex Reflex Cardiac Stimulation

Figure 1 Hemorrhage reflex response

THE RESERVE THE PERSON NAMED IN

Systemic Vasoconstriction

Flow & Volume Redistribution

Figure 2 Hemorrhage humoral responses

Vasoconstriction

Increased Volume

Cardiac Stimulation

### Septic Shock

- There is systemic vasodilation (hypotension) and fever
- Most common site for infection leading to sepsis is lung
- Most common cause of sepsis is gram-positive organism----65%
- Lipoteichoic acid is the most important factor producing septic shock in gram-positive pathogens
- E-coli is the most common cause of gram-negative septic shock—25%
- Most common fungal cause of septic shock is Candida---9%

### Clinical features:

- ✓ In septic shock, the skin may be warm and flushed as a result of peripheral vasodilation
- Heart rate: Tachycardia
- Bounding pulse, due to increased cardiac output
- Skin is pale and dry
- ✓ JVP is low in septic shock
- ARDs: due to neutrophil transmigration into alveoli
- DIC: due to activation of the intrinsic and extrinsic coagulation system

### Cardiogenic Shock

- Cardiogenic shock results from failure of the cardiac pump
- MI is the most common cause
- Distended jugular veins due to increased jugular venous pressure
- Weak or absent pulse
- Abnormal heart rhythms, often a fast heart rate
- Reduced blood pressure and pulmonary capillary wedge pressure or PCWP is >15 mm Hg

### **Blood Groups**

- HLA gene is on chromosome 06
- ABO gene is on chromosome 09
- ABO blood group is an example of Codominance
- ABO blood types in human is determined by three alleles
- D Bombay blood group:
  - ✓ The antigen present on "O" group red cell is the "H" substance, which is the precursor of A, and B antigens.
  - ✓ Absence of "H" substance leads to a rare blood group termed that is the Bombay blood group designated as "Oh". These individuals have anti-A, anti-b and anti-H antibodies and thus can receive blood only from individuals with Bombay blood group
- MNS blood group:
  - ✓ MNS blood groups are determined by their reaction with Anti-M, Anti-N and Anti-S.
  - ✓ These blood group rarely causes hemolysis following transfusion
- Rh factor:
  - Present in RBC, many Rh antigens are present but only the Rh D is the most immunogenic antigen

Group	Antigen on red cells	Alloantiboides in plasma
A	A	Anti- B
В	В	Anti- A
0	SO OF HALL	Anti-A, Anti-B
AB	A,B	None

- Blood group with no agglutinin-
- Most severe reaction-----
- Adverse blood transfusion occurs in-----AB to A+
- Universal recipient-----AB+
- Universal donor-----O, if there is insufficient time to do cross matching of blood, this type of blood should be used
- O' Is 37% in Caucasians and 39% in the Asian population, O' Is 8% in Caucasians and 1% in Asian population
- Positive can donate blood to positive only while negative can donate blood to both positive and negative
- Mother blood group A, one child O and other child AB, father will have blood group ----B
- When blood must be given in emergency, Group O is given, O-negative = to female, O positive= to male

# Shock, Blood Transfusion & Transplantation



### **Blood Transfusion Reaction**

The most common cause for a major hemolytic transfusion reactions is a clerical error (Human error), such as mislabeled specimen sent to the blood bank, or not properly identifying the patient to whom you are giving the blood.

### Allergic reaction:

Chapter 28

- Type 1 hypersensitivity reaction---against plasma protein of transfused blood
- Clinical features:
  - ✓ Urticaria
  - Pruritis, itching commonly at infusion site
  - Wheezing
  - ✓ Fever
- Treatment: stop, observe and antihistamine
- Anaphylactic reactions
  - Severe reaction
  - IgA deficient individuals must receive blood products that lack IgA
  - Clinical features:
    - Dyspnea, bronchospasm, hypotension, respiratory arrest and hypotension
  - Treatment: stop the transfusion, Epinephrine and IV fluids
- P Febrile non-hemolytic reaction
  - Type II hypersensitivity reaction
  - Host antibodies against donor HLA antigen and leukocytes
  - Clinical features
    - √ Fever
    - √ Headache
    - ✓ Chills and flashing
- Acute Hemolytic Transfusion Reaction (AHTR)
  - Type II hypersensitivity reaction
  - Clinical features:
    - ✓ Fever, important early sign
    - ✓ Hypotension, rapidly leading to shock
    - ✓ Tachypnea
    - √ Tachycardia and Flank pain
    - ✓ Bleeding at transfusion site
  - In anesthetic patient:
    - ✓ Tachycardia, hypotension and oozing from the surgical site
    - ✓ Acute hemolytic transfusion reaction due to transfusion of incomputable blood in
    - a patient under general anesthesia usually presents as generalized bleeding due to DIC. The most specific tests to determine hemolysis are free plasma hemoglobin and Hemoglobinuria
  - Treatment:
    - √ Stop transfusion
    - ✓ Hydration to maintain urine output > 100ml/hour
    - Diuresis with Mannitol to prevent renal failure

### **Blood Loss**

- In Vaginal delivery, normal blood loss: 500 ml, C-section blood loss: 1000ml
- Normal blood loss during the first week PP is another—800ml
- Return to non-pregnant circulating volume in—3-4 week post-delivery
- Shock occurs when---->20% or = 1000ml blood volume loss and there is no change occur when blood loss is about 500ml
- 10-15 % blood loss should be replaced by——Ringer lactate (R/L)
- Normal menstrual flow is --- < 80 ml</li>
- After hemorrhage protein return to normal in 2-3 days and RBC return in the last—4-8 weeks
- Least lymphatic flow is due to hemorrhage.
- After moderate hemorrhage, the circulating plasma volume is restored in 12-72 hours. Performed albumin also enters rapidly from extravascular stores, but most of the tissue fluids that are mobilized are protein-free. After the initial influx of performed albumin, the rest of the plasma protein loses are replaced, presumably by the hepatic synthesis, over a period of 3-4 days or 2-3 days
- Strong bedside predictors of moderate Hypovolemia from blood loss are postural dizziness so severe as to prevent standing and a postural pulse increment greater than 30 beats per min but the sensitivity of these finding is only 22%
- The Best measure of blood loss estimation is the weight of soaked gauze
- A hemoglobin level of 6g/dl is acceptable in patient who are not actively bleeding, not about to undergo major surgery and are not symptomatic

# Class of Acute Hemorrhage Class I hemorrhage:

- Involves up to <15% or 750ml of blood volume</li>
- There is typically no change in vital signs and fluid resuscitation is not usually necessary

### Class II hemorrhage:

- Involves up to 15-30% 750-1500ml or of blood volume
- Volume resuscitation with R/L is typically required, Blood transfusion is not usually required

### Class III hemorrhage:

- Involves up to 30-40% or 1500 to 2000ml of blood volume
- Fluid resuscitation with crystalloid and blood transfusion are usually necessary

### Class IV hemorrhage:

- Involves up to >40% or >2000ml(>2L)of blood volume
- The limit of the body compensation is reached and aggressive resuscitation is required to prevent death

Chapter 28

Shock, Blood Transfusion & Transplantation

## Transplantation

"It is infinitely Better to Transplant a Heart Than To Bury it to be Devoured by Worms"

### **Basic Definitions**

Graft	Graft are tissues that are transfer without their blood supply, which therefore have to re-vascularis once they are a new site		
Flap	Flaps are tissues that are transferred with a blood supply. They are therefore have the advantage of bringing vascularity to the new area		
Free Flap	The blood supply has been isolated, disconnected and then reconnected using microsurgery at the new site		
Auto-graft	from self, the best survival rate		
Syngeneic graft or isograft	from identical twin of clone, it is always accepted		
Allograft	from non-identical individuals of same species		
Xenograft	from different species		
Orthotopic graft a graft placed in its normal anatomical site			
Heterotopic graft	A graft placed in a site different from that where the organ is normally located		

### Naseem Sherzad High-Yield Points

- · Cornea transplant is the most successful transplant
- Mild transplant rejection----lymphocyte
- \* ABO blood grouping is the single most important prerequisite for successful transplantation
- HLA-------Human leukocyte antigen, the main trigger of graft rejection and thus HLA is the most important for transplant
- For Bone marrow transplant HLA is more important as they lack ABO system
- Initial test/investigation, sample required is WBC
- For kidney transplant, HLA-1 is more important
- The most common reason for skin graft failure is hematoma beneath the graft
- HLA typing in renal transplant decreases the activation of CD8
- There is no need of immunosuppressant drugs for graft taken from an identical twin
- Antigen-antibody reactions are most reduced in liver failure
- \* Tissue taken for HLA typing is leukocyte

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Shock, Blood Transfusion & Transplantation

### **Transplant Rejection**

Complications

### Infection:

- Transplant recipients are a high risk of opportunistic infection, especially by viruses
- Viral infection may result from reactivation of latent virus or from primary infection
- CMV is the most common infection in transplant patient.
- CMV doesn't not predispose transplant patient to malignancy
- Candida albicans is the most common infection in solid organ transplantation
- The risk of bacterial infection is highest during the first month after transplantation
- Pneumocystis carinii is the most common Protozoal infection seen after transplantation, It occurs during the first few months post after transplantation and present with respiratory symptoms

### Malignancy:

- After transplantation, there is an increased risk of developing most type of malignancy but the risk is particularly high for those type of tumor in which viral infection plays an etiological role
- The risk is particularly high for skin cancer and a condition called post-transplant Lymphoproliferative disorder (PTLD). Most of the skin cancers
- PTLD are associated with EBV

### The Incidence in renal transplant:

- Lymphocele—50% ————The most common
- Renal artery thrombosis----<1%</li>
- Renal vein thrombosis----<1%

### Hyperacute:

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- Within minute
- Anti-body mediated and irreversible-----type 2 hypersensitivity reaction
- Hyperacute rejection is irreversible and involves antibody
- " It is due to the presence in the recipient of Pre-formed antibodies against HLA- class 1 antigen. It can also occur due to ABO-blood group incompatibility
- Kidney transplants are particularly vulnerable to Hyperacute rejection, Heart and liver transplant are relatively resistant
- Occlude blood vessels, cause ischemic necrosis
- There is no therapy for Hyperacute rejection

### Acute:

- It usually occurs during the first 6 months (typically between first week and 3 months)
- Cell-mediated to CTLs reacting against foreign MCHs
- It is <u>Reversible</u> with <u>immunosuppressant</u> and is the most common transplant rejection

### Chronic:

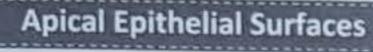
- Months to year
- Class 1-MHCs non-self is perceived by CTLs as a class 1-MHCs self-presenting a non-selfantigen
- Irreversible
- It is the most common cause of allograft failure
- The liver appears to be more resistant than other solid organs to the destructive effects of chronic rejection
- T-cell and antibodies mediated vascular damage

### Graft-versus-host

- \* Grafted Immunocompetent T cell proliferate in the irradiated immunocompromised disease host and reject with "foreign" proteins resulting in severe dysfunction
- Usually occur in bone marrow and liver transplant
- Present with following features:
  - ✓ Maculopapular rash
  - √ Jaundice
  - ✓ Hepato-splenomegaly and diarrhea

# HISTOLOGY





#### Microvilli:

- Small, slender, finger-like projection found on the free surface of epithelial cells —about 1-2um in height, 0.1um diameter
- Example and function:
  - ✓ They greatly increase the surface area and help in absorption
  - The Epithelial lining of the small intestine and gallbladder
  - ✓ The Epithelial layer of PCT

#### Cilia:

- These are hair-like active motile process found chiefly on the free surface of those epithelial cells which are specialized for transport of fluid or mucus over the epithelial surface---about 5-10um in height, 0.2um diameter
- Cilia contain the highest amount of mitochondria at the apex
- Cilia contain an axoneme with ciliary dynein arm extending unidirectionally from one member of each doublet. Ciliary dynein has ATPase activity.
- Axoneme consist of nine doublet microtubules uniformly spaced around two central microtubules (9+2 configuration)
- Basal body consist of----(9+0 configuration)
- Defective ciliary function is associated with bronchiectasis e.g. Kartagener's syndrome in which there is Absent or irregular dynein arms (motor part) of cilia
- Example and function:
  - Respiratory epithelium
  - The Epithelial lining of uterine tube and uterus

#### Flagellum:

- This is long, motile, whip-like projection from a cell.
- Example and function:
  - ✓ The only cell that possesses flagellum is sperm, average length 55um
  - Produce undulating movement that helps in locomotion of the whole cell

#### \* Stereo-cilia:

- . These are nothing but extremely long Microvilli (not cilia), resembling cilia, average length, 30um
- Example and function:
  - ✓ Chiefly found on cell lining Epididymis, in Epididymis increase surface area to help. reabsorption
  - ✓ Also found on the neuroepithelial and sustentacular cell of taste buds and hair cell of the internal ear

Chapter 29

	Histole
Simple Columnar Epithelium	Simple Squamous Epithelium
<ul> <li>Cells in the simple columnar epithelium are joined by tight junction</li> </ul>	<ul> <li>Consist of a single layer of <u>flat cell</u> lying or</li> </ul>
* Examples	a BM <b>❖ Example:</b>
# GITNon ciliated	■ Endothelium: Which cover the interna
# Gall bladderNon-ciliated	surface of heart, blood vessels and
<ul> <li>Uterus and fallopian tube (whip-like</li> </ul>	lymphatics
moment)Ciliated	<ul> <li>Mesotheliom—lines the pericardial</li> </ul>
Spinal cord and choroid plexus of the	pleural and peritoneal cavities
ventricle	Alveolar epithelium
* Endocervix	

Simple Cuboidal Epithelium	End arteries	
<ul> <li>Ovary</li> </ul>	End arteries present in vital organs like	
Small duct of many gland	- Retina	
<ul> <li>Distal convoluted tubules of Nephrons</li> </ul>	Spleen	
	Heart	
	Orderretina > spleen> heart	

NOTE: Detailed histology and various types of epithelium are given system wise respective Chapters

#### Pseudo Stratified Columnar Epithelium

- All the cells rests on base
- Consist of a single layer tall cells that gives a false impression of being stratified because the nuclei are at different levels

#### PTCL:

- P-----Pulmonary bronchi, Prostate, Pharyngeal tonsil, Vas deferens (ductus deferens)
- T-----Trachea
- C-----Ciliated cavity, Nose
- L-----Larynx-----False vocal cord

## PTCL is also for Chlamydia infection: causing

- P—PID---Chlamydia is the most common cause of PID
- T—trachoma
- C---Chlamydia itself
- L---lymphogranuloma venereum

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NASEEM SHERZAD FCPS -1 HIGH-YIELD

Histology

## Histology

#### Dense connective tissue

#### Dense regular connective tissue:

- Fibers are densely packed and arranged parallel to each other
- Fibroblasts are the only cell type present in very small number as elongated and flattened
- Usually occur in the form of tendons, ligaments and aponeurosis
- Some ligaments are composed of almost entirely of elastic fiber, called yellow elastic ligament e.g. vocal cords, ligamentum flavum of the vertebral column and suspensory ligament of the penis

#### Dense irregular connective tissue

- The fibers usually occur in the form of sheets
- Consist of mainly of collagen fiber but other fibers are also present
- Some fibroblast and macrophages are found between the fibers
- Example
  - ✓ Dermis of skin
  - The capsule of organs (e.g. liver, testis, lymph nodes)
  - Perichondrium
  - ✓ Periosteum

#### What is Fibroblast:

- Fibroblast, the principal active cell of connective tissue.
- Fibroblasts are large, flat, elongated (spindle-shaped) cells possessing processes extending out from the ends of the cell body. The cell nucleus is flat and oval.
- Fibroblasts produce tropocollagen, which is the forerunner of collagen, and amorphous ground substance that fills the spaces between cells and fibers in connective tissue.

#### White fat and Brown fat

#### Brown fat:

- This fat is composed of several small lipid (fat) droplets and a large number of ironcontaining mitochondria (the cell's heat-burning engine).
- The iron, along with lots of blood tiny blood vessels, gives this fat its brownish appearance.
- Brown fat is usually found in the front and back of the neck and upper back.
- The purpose of brown fat is to burn calories in order to generate heat. That's why brown fat is often referred to as the "good" fat, since it helps us burn, not store, calories.
- Exposure to cold temperatures causes stem cells to form brown fat instead of white fat

#### White fat:

- This type of fat is composed of a single lipid droplet and has far less mitochondria and blood vessels, thus resulting in its lighter white or yellow appearance.
- White fat is the predominant form of fat in the body, originating from connective tissue.
- It provides the largest energy reserve in the body. It's a thermal insulator and cushion for our internal organs, and cushions during external interactions with our environment (that's code for a soft landing when we fall on our behind!). It is a major endocrine organ, producing one form of estrogen as well as leptin, a hormone that helps regulate appetite and hunger. It's also got receptors for insulin, growth hormone, adrenaline, and cortisol (stress hormone).

Thymus

- It is bilobed organ derived from the endoderm of the third brachial pouches
- Richest in lymphocyte, lymphocyte are of mesenchymal in origin
- There is no lymphatic nodules, no germinal center in the thymus
- Thymoma located in the anterior mediastinum
- During development, T- cells are protected from immunological attack by blood thymus barrier
- Regress after puberty, atrophy occur

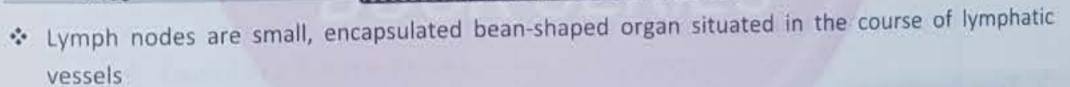
#### Cortex:

- ✓ Positive selection occurs in cortex---MHC protected
- Cortex is dense with immature T-cell
- T-cell maturation occur
- Immature T-cell are called thymocyte
- Blood thymus barrier is present only in cortex making it immunologically protected region
- √ 90% of developing T-cell dies in cortex because of improper selection (apoptosis)

#### Medulla:

- ✓ Negative selection occurs here means non-reactive to itself
- ✓ The medulla is pale with mature T-cell and epithelial reticular containing Hassal's corpuscle.
- ✓ Epithelioid reticular cell aggregates and Hassal's corpuscle (function of this is unknown)
- ✓ Mature T-cell exit the thymus via Venules and efferent lymphatic vessels to secondary. lymph node

#### Lymph Node



#### Cortex:

- Lies deep to capsule from which it is separated by a <u>subcapsular sinus</u>.
- ✓ The subcapsular sinus is lined by a layer of endothelial cells. Beneath the endothelial cells. are macrophages that retrieve antigen from the lymph in the subcapsular sinus. These macrophages cannot be distinguished in histological images.
- ✓ Contain lymphoid nodules, sinus and Paracortex
- ✓ Paracortex: it is the deep cortex which is devoid of the lymphoid nodule. Here the cells are mostly T-cells

#### Medulla

- ✓ Lies deep to Paracortex
- ✓ It is composed of Medullary sinus and Medullary cords

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NASEEM SHERZAD FCPS -1 HIGH-YIELD

THEY

#### Collagen

- Most abundant protein in the human body
- Extensively modified by post-transitional modification
- Organizes and strengthens extracellular matrix
- Thyroxin, testosterone, somatotropin——Stimulate cartilage histogenesis
- · Cortisone, hydrocortisone, Estradiol-----Inhibit cartilage histogenesis

#### Various Types

#### Type I Collagen:

- Type I collagen is the most abundant collagen (90%) of the human body which forms large, Esoinophillic fibers known as collagen fibers.
- Form Triple helix
- Increasing the strength of wound and resistance to tension is function of collagen type I
- Predominant in scar
- The remodeling phase is characterized by maturation (type I replacing type III until a ratio of 4:1 is achieved)
- Example:
  - ✓ Bone (made by osteoblast)
  - ✓ Skin and mature Scar
  - ✓ Tendon
  - ✓ Late wound repair
  - √ Cornea
  - ✓ Dentin and fascia

#### Type II collagen:

- Type I and II are called fibrillar collagen
- Example:
  - ✓ Elastic cartilage
  - ✓ Hyaline cartilage
  - ✓ Vitreous body
  - ✓ Nucleus pulposus

#### Type III collagen:

- Present in immature tissue
- Laid down first in wound healing
- Example
  - √ Fibrocartilage

#### Chapter 29

Histology

- ✓ Granulation tissue
- ✓ Early scar
- Reticular fiber----liver spleen and lymphoid organs like tonsil
- Early wound healing
- √ Large vessels
- √ Keloid
- ✓ Uterus and fetal tissue

#### Type IV collagen:

- Basement membrane or basal lamina (Under the floor)
- Epithelium with no basement membrane is Ependyma
- Important to Note:
  - The lamina rarae contains Heparan sulfate, a Polyanionic glycosaminoglycan that assists in restricting the passage of negatively charged protein into the bowman space. The negatively charged glomerular basement membrane prevent or restrict the filtration of molecules such as albumin and other highly negatively charged molecules
  - The lamina densa contain type IV collagen, which acts as a selective macromolecular filter preventing of large molecules into the bowman space

#### Naseem Sherzad High-Yield Points

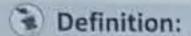
- Type I defective in-----Osteogenesis imperfecta
- Type III defective in-----Ehlers-Danlos syndrome
- Type IV defective in------Alport syndrome
- Type IV targeted by autoantibodies in----Good Pasture syndrome
- Caused by a defect in fibrillin-------Marfan syndrome
- Sesamoid cartilage: ------Ala of nose (sesamoid cartilage of larynx: a small nodule of elastic cartilage sometimes presents on the lateral border of the Arytenoid cartilage)
- Sesamoid bone:------Patella, Pisifrom, Fabella (fibula and fabella are two different things)

#### Collagen Types

- . Collagen one-----bONE (main components of bone)
- Collagen Two----carTWOlage (main components of cartilages)
- Collagen Three----reTHREEculate (main components of reticular fibers)
- Collagen four-----FLOOR (forms the basement membranes)

THIGH-AILS

#### Cartilage



Cartilage is a specialized type of dense connective tissue designed to give support, bear weight and withstand tension, torsion and bending

#### Classification/types of Cartilage

#### Hyaiine Cartilage:

- Most abundant
- Has a high proportion of amorphous matrix that has the same refractive index as the fibrous embedded in it
- Hyaline cartilage is incapable of repair when fracture, the defect is filled with fibrous tissue
- Collagen fibers are not visible under the microscope
- These are the precursor for endochondral bone formation

#### Elastic Cartilage:

- Appear yellowish when fresh because of abundant of elastic fiber
- Most thick in the aorta
- Elastic cartilage if damaged repair itself with fibrous tissue
- Example
  - ✓ Ear pinna
  - ✓ External auditory tube
  - ✓ Epiglottis
- Note that the vagina contains elastic fiber

#### Fibrocartilage:

- No perichondrium
- Has many collagen fibers embedded in a small amount of matrix
- Fibrocartilage, if damaged, repair itself slowly in a manner similar to fibrous tissue elsewhere
- It is type I collagen
- Example:
  - ✓ TMJ and Intervertebral disc
  - ✓ Menisci of knee
  - ✓ Pubic Symphysis
  - ✓ Acetabular and glenoid labrum
  - ✓ Articular disc

# COMMUNITY 3 COMMUNITY MEDICINE

#### **Biostatistics**

The science of collection, processing, classification, presentation, quantification, analysis, organizing, summarizing, dissemination and interpretation of data related to vital events is called biostatics <u>OR</u>

A subject that deals with collection, presentation, analysis and interpretation of data

#### Population, Sample and Sampling

- Population: Defined as "The whole set of things about which we want to know". In statistic, population can be human beings, table, chairs, rice, ECG machine and Inderal tablet etc.

  OR a population is the universe about which an investigator wishes to draw the conclusion
- Sample: A part taken out of the population for the actual study is called sample
- Sampling: When some members of the population are drawn for examination

#### Random sample:

Defined as where each and every member of the population has an equal chance of selection

#### There are two types

- i. Probability sampling
- ii. Non-probability sampling
- 1. Probability sampling types: MSC...3S
- a) Simple sampling
- b) Systemic sampling
- c) Stratified sampling
- d) Cluster sampling
- e) Multistage sampling
- II. Non- probability sampling:
  - a) Purposive sampling
  - b) Convenience sampling
  - c) Quota sampling
  - d) Snowball sampling

#### Naseem Sherzad High-Yield Points

Collected from FCPS Part-1 Past papers

- Chi-square: Association between two variables, compare percentage or proportion of categorical
- Regression analysis: Co-relation between two variables
- t-test: Check the difference between two means of 2 groups. Mr. T is Mean
- ANOVA: Check the difference between the mean of 3 or more groups---ANOVA: ANalysis Of VAriance of 3 or more groups
- Equity "In health care is closely related to the principle of bioethics Justice"
- The Sick role involves: Being excused from the various obligation
- Kaplan-Meier estimator, also known as the products limit estimator, is a non-parametric statistic used to estimate the survival function from lifetime data
- Patient experience stress of hospitalization due to the structure and functioning of the hospital
- For doctor In OPD active listening should be present in order for best communication with the patient
- Sociology is the branch of behavioral science
- Confidentiality can be breached if the patient allows you
- The Myer-Briggs Type Indicator (MBTI) Created by Katherine Briggs and daughter Isabel Myers, the MBTI is one of the most popular personality assessment tests to date.
- Health: It is a state of complete physical, mental and social wellbeing and ability to functions and not the mere absence of disease or infirmity, and ability to lead a socially and economically productive life.
- Symmetry: now skew
  - ✓ Two tail or no tail
  - ✓ Important example: the normal curve
- Positive skew or right skew: Characteristic
  - ✓ Peak on left
  - ✓ Long right tail----Stretch (Skewed) to the right
  - ✓ A few large values
- Negative skew or left skew: Characteristic
  - ✓ Peak on right

THE RESIDENCE AND RESIDENCE

- ✓ Long left tail----Stretch (Skewed) to the left
- ✓ A few small values

#### IMPORTANT NOTE FOR SOLUTION OF NUMERICAL

- Now the most important question, how do we find if the scenario is of cohort study or casecontrol study?
- \* The answer is very simple, if the disease is there and they ask you to study whether any risk factor is related to it or not it's most probably CASE CONTROL STUDY. If the risk factor is there and they ask you, to FOLLOW UP whether the disease will occur or not, it's a COHORT STUDY.
- \* Very simple: when risk factor and outcome is given=case control study and when cause and effect is given=Cohort Study
- And when matching/comparison is given in question go directly for case-control study.
- In cohort study first step: Divide the patient in exposed and non-exposed. 2<sup>nd</sup> step: Then follow to see whether diseases develops, disease dose not develop

Data and its type

Data:

Data are the actual pieces of information that you collect through your study

Types of Data/variable:

Data consist of the variable. We need to know different types of the variable because different techniques are used to analyze different variable

1) Categorical data:

Categorical data represent characteristics such as a person's gender, marital status, hometown, or the types of movies they like. Categorical data can take on numerical values (such as "1" indicating male and "2" indicating female), but those numbers don't have mathematical meaning. You couldn't add them together, for example. (Other names for categorical data are qualitative data, or Yes/No data.

#### Subtypes:

- i. Nominal data: observation have name only, for example male/female, black/ white, absent/ present, yes/ no yellow/brown etc. There is no order or ratio.
- ii. Ordinal data: when categorical data can be arranged in ascending or descending order OR when data placed in a meaningful order

#### 2) Numerical data:

These data have meaning as a measurement, such as a person's height, weight, IQ, or blood pressure; or they're a count, such as the number of stock shares a person owns, how many teeth a dog has, or how many pages you can read of your favorite book before you fall asleep. (Statisticians also call numerical data quantitative data).

Numerical data can be further broken into two types:

i. Discrete: when items can be counted e.g. number of children a women gives birth to. They can 1, 2, 3 or 4 and even more. It can't be 2.6

ii. Continuous:

Continuous data can be further broken into:

- a) Interval: The categories are arranged in equally spaced units and there is no absolute zero. Temperature on Celsius scale is interval scale. But temperature of 10 centigrade does not means that it is twice as hot as a temperature of 5 centigrade because Celsius scale does not have true zero point.
- b) Ratio: This is an interval scale with true zero point e.g. Age, weight and blood, a student weighting 80kg is twice as heavy as a student of 40 kg

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NAME AND POST OFFICE ADDRESS OF

Chapter 30

#### Hypothesis

Statement based upon the assumption that may or may not be true is called a hypothesis.

Any statement about a population is termed as a hypothesis

- \* Types: There are two types of hypothesis
  - a) Null hypothesis/hypothesis of no difference:

Any hypothesis, which has to be tested for a possible rejection or nullification under the assumption that is true i-e there is no difference between the effects of two vaccines. OR Null hypothesis claim that there is no relationship (difference) between two groups being compared and denoted by Ho

E.g. if we want to know the complication rate of two surgical procedures for hysterectomy (removal of the uterus) Abdominal hysterectomy and vaginal hysterectomy. Null hypothesis will claims that there is no difference between the two surgical procedures with respect to postoperative complication.

b) Alternate hypothesis: it states that the different sets of data belong to different populations are statistically significant and are not due to chance. In other words:

- Steps in testing hypothesis:
  - State the null and alternate hypothesis, Ho and HA
  - Select the decision criterion alpha (or "level of significance")
  - Establish the critical values.
  - Draw a random sample from the population and calculate the mean of that sample.
  - Select an appropriate statistical test and compute the value of the test statistic Z or X' (as the case may be)
  - Compare the calculated value of test statistics with critical values of Z/t/X2 and then accept or reject the null hypothesis.

#### Type 1 and Type 2 Error

#### Type 1 error OR alpha error:

The incorrect rejection of a true Null hypothesis is called type 1 error.

Example:

A test that shows that a patient to have a disease when in fact the patient does not have the disease

#### Type 2 error OR beta error:

It is the failure to reject a false null hypothesis

Example:

Blood test failing to detect the disease it was designed to detect in the patient who really has the disease.

**Community Medicine** 

Measures of Central Tendency

Average—"Single central valve, which is intended to represent the whole distribution or whole set of data" such central value is called average. Kinds of average or central tendency

- Arithmetic mean: It is the valve, which is obtained by dividing the sum of all observations by their total number. Denoted by  $\bar{X}$
- Median: "The middle most item of data is called median". To obtain the median:
  - ✓ Arrange data in an ascending or descending order
  - ✓ If the total number of observations or data is an odds number, then the middle item is the median.
  - ✓ If the total number of observations or data is an even number, then find median by taking. the average of the middle two values.
  - ✓ Example find the median of: 20, 20, 25,25,30,30,35,40: the median of the given date is 27.5
- Mode: "The most commonly occurring value in a data is called mode".

#### Measures of dispersion

- \* Range: It is the simplest measure of dispersion and is defined as "difference between the highest and lowest figure in a given samples".
- . Mean deviation: "It is the average of the deviation from the arithmetic mean"
- Standard deviation: It is also called root mean square deviation and defined as "the positive square root of the arithmetic mean of square deviation from the mean of distribution" or SD is the square root of the variance
- Variance: it tells us how spread out the data is, telling us about variability

#### Standard Error

Standard error: "The standard error (SE) is the standard deviation of the sampling distribution of a statistical mean".

- Used as an instrument in testing a given hypothesis
- The variation or dispersion of the distributions of a sample means is measured by Standard error.
- If we take a random sample from the population and similar samples over and over again, we will find that every sample will have a different mean.
- Formula: The SD of mean is the measure of SE

  - √ n = Sample size
  - $\checkmark \sigma$  = Sigma= Standard deviation

## Various methods of presenting quantitative and qualitative data Methods of presenting quantitative and qualitative data:

#### A. Tables

- ✓ Simple tables
- ✓ Frequency distribution tables

#### B. Charts and diagrams

- ✓ Bar chart
- ✓ Pie chart
- √ Histogram
- ✓ Frequency polygon
- ✓ Line diagram:
  - o It is used to show the trend of the event with the passage of time.
- ✓ Scattered diagram:
  - o This is the best method for comparing the relationship between two variables like change in plasma renin level with change in BP
- C. Graphs
- D. Pictures
  - Pictograms: pictogram is popular method of presenting the data to the "man in the street" and those who can't understand orthodox charts

#### **Chi-Square Test**

#### Chi-square test:

Chi-square (X<sup>2</sup>) test offers an alternate method of testing the significance of the difference between two proportions. It has the advantage that it can be used when more than two groups can be compared.

### Steps of chi-square test:

- Testing the null hypothesis
- Application of the X2 test
- Finding the degree of freedom
- Looking into the probability tables

#### Formula:

$$\chi^2 = \sum \frac{(O - E)^2}{E}$$

#### Here,

- O = Observed frequency
- E = Expected frequency
- ∑= Summation
- X<sup>2</sup> = Chi-Square value
- R= Row and C= column



Sensitivity, Specificity and Predictive value



Sensitivity:

This topic is very important for FCPS Part-1 Exam

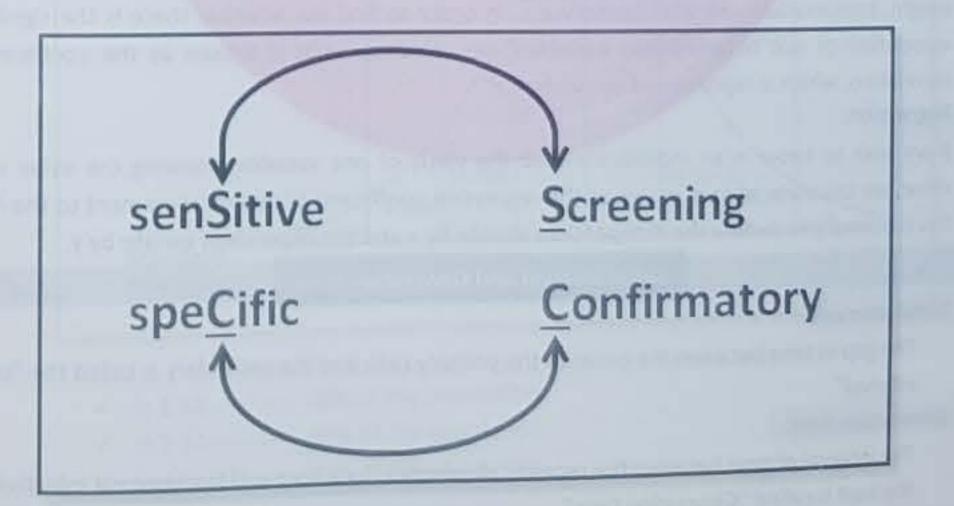
- " It is defined as the ability of the test to identify correctly all those who have the disease, that is "true positive" OR ability of test to rule out disease
- A test with 100% sensitivity will recognize all patients with disease by testing positive
- A negative test would definitely rule out the presence of the disease in a patient.
- \* A sensitive test is used for excluding a disease, as it rarely misclassifies those WITH a disease as being healthy.
- Able to both diagnosis and eliminate diseased and non-diseased
- Detect all those with disease in the screen population

#### Specificity:

- \* It is defined as the ability of the test to identify correctly all those who do not have the disease, that is "true negatives". Ability to rule IN disease
- \* A specific test is used for ruling in a disease, as it rarely misclassifies those WITHOUT a disease as being sick.
- Identify correctly all those without diseases means free of disease in the screened population

#### Mnemonic

- SNOUT: Very sensitive test +result is not very helpful, but -result is useful-Rule disease OUT
- \* SPIN: Very specific test -result is not very helpful, but +result is useful----Rule disease IN



- Predictive Value As pointed out previously, sensitivity and specificity define the discriminative power w diagnostic procedure (test) and give us the proportion of diseased and healthy individually identified correctly by the test, respectively. However, sensitivity and specificity tell us not about the predictive abilities of a positive or a negative result.
- What a physician wants most from any diagnostic procedure is the answer to the follow-

"If a person has a positive test result, how sure can I be that this person has a disease? If a person has a negative test result, how sure can I be that this person to

- Very useful measures of diagnostic accuracy, which give answer to these questions, and predictive values: positive predictive value (PPV) and negative predictive value (NPV).
- Positive predictive value (%) defines the probability of the disease in a person who has a positive test result. It represents the proportion of the diseased subjects with a positive test results in true positives) in a total group of subjects with positive test results (TP/(TP+FP)). Therefore positive predictive value relates to the predictive ability of a test to identify disease in individual
- Negative predictive value (%) defines the probability of the absence of the disease in a person who has a negative test result. It indicates the proportion of healthy subjects with negative test results (TN, true negatives) in a total group of subjects with negative test result (TN/(TN+FN)). Therefore, negative predictive value relates to the predictive ability of a test to identify the absence of the disease in individuals with negative test results.

# Difference between Correlation and Regression

#### Correlation:

Often we wish to know whether there is a linear relation between two variables e.g. height and weight, temperature and vital capacity etc. in order to find out whether there is the significant association or not between two variables, we calculate what is known as the coefficient of correlation, which is represented by symbol "r" Regression:

If we wish to know in an individual's case the value of one variable, knowing the value of the other, we calculate what is known as the regression coefficient of one measurement to the other. It is customary to denote the independent variate by x and the dependent variate by y.

## Serial interval and Generation time

The gap in time between the onset of the primary case and the secondary is called the "serial

#### Generation time:

Serial interval:

The interval of time between the receipts of infection by a host and the maximal infectivity of

## Chapter 30

Community Medicine

#### Normal Distribution Curve

Also known as, Gaussian distribution A British mathematician De Moivre conceived it first in the seventh century. It is important statistical distribution and is a mathematical model of the frequency distribution of most biological valves in nature. Shown diagrammatically the standard normal distribution is denoted as a curve known as normal curve or Gaussian curve.

On the X-axis are the valves and the Y-axis shows the frequency of those values like a frequency distribution. It is important to remember that normal distribution is a probability distribution and is an ideal world. If our collected data has tendency to conform normal distribution then we make use of it in statistical inference. The total probability of frequency of valves under the curve is equal to 1 or 100%. ALL the individual values under the curve have the probability of occurrence (frequency) ranging between 0 and 1 (0 to 100%) and total to 1.

#### Properties of the standard Normal Curve

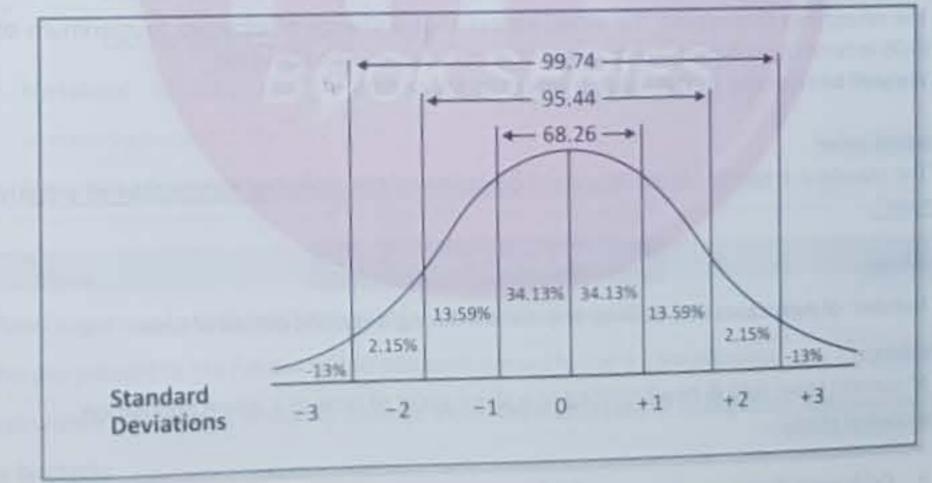
- It is bell-shaped
- It is perfectly symmetrical

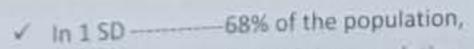
- Mean, median, and mode are in the center of the curve i-e. The dome of the curve.
- Half the value (50%) lies on each side when it is cut into half at the highest point.
- It has got two determinants Mean and Standard deviation
- Total area is 1
- SD is 1

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. The mean is zero





- ✓ In 2 SD----95% of the population
- ✓ and in 3SD----99% of the population

#### **Level of Prevention**

Mnemonic PDR

Primary:

- Prevent: Prevent disease occurrence
- Mode of intervention:
  - ✓ Health promotion
  - ✓ Specific protection: HPV vaccination, immunization, Prophylactic administration of vitamin K in breast-fed babies, measure for prevention of dental caries like fluoride dentifrices, intake of sufficient fluoridated water and brushing

Secondary:

- Detect: Early detection of disease
- Example Pap Smear, Breast Self-Examination

Tertiary:

- Reduce disability: Reduce disability from disease
- Example: Chemotherapy

Latent period:

 The term latent period is used in non-infectious disease as the equivalent of the incubation period in infectious disease. Remission of symptoms



#### Important Definitions



What is P-value? P-value stand for "Probability value"

- The probability of committing type 1 error (means rejecting of H<sub>o</sub> when actually it was true) is known as p-value.
- The researcher throughout the world agrees that a chance of error up to maximum of 5% (0.05 in term of probability) is reasonable in making decision about Ho.
- We well be rejecting H<sub>o</sub> if P-value is less than 5% or 0.05

Standard error

"The standard error (SE) is the standard deviation of the sampling distribution of a statistical mean".

**Incidence** 

Number of new cases in a defined population during a specific period of time

Prevalence:

· All current cases (old & new) existing at a given point of time in a given population

Case-control study:

• Odds ratio (cross products) =  $\frac{a \times a}{b \times c}$ 

Cohort study:

- Relative Risk = incidence among exposed/incidence among non-exposed
- Attributable Risk = incidence among exposed-incidence among non-exposed/incidence among exposed

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# NASEEM SHERZAD HIGH-YIELD POINTS

Fluids and Electrolytes

- Liver Cirrhosis and Portal Hypertension: Metabolic alkalosis
- Pyloric stenosis: Hypochloremic, hypokalemic metabolic alkalosis with paradoxical aciduria is the classic electrolyte and acid-base imbalance of pyloric stenosis
- Ureterosigmoidostomy: Hyperchloremic hypokalemic metabolic acidosis
- There is Metabolic acidosis with normal anion gap in intestinal fistula and severe diarrhea
- Most common using crystalloid: Ringer lactate (R/L)
- \* Fluid of choice for Burn patient: R/L
- Fluid of choice in patient of Entero-cutaneous fistula: R/L
- Fluid Composition:
  - Normal Saline: Sodium: 154 mEq/L, Chloride: 154 mEq/L: Potassium: 0 mEq/L, Lactate: 0 mEq/L
  - Ringer Lactate: Sodium: 130 mEq/L, Chloride: 109 mEq/L, Potassium: 4 mEq/L, Lactate: 28 mEq/L
- Metabolic acidosis with normal anion gap occur in all type of fistula and ureterosigmoidostomy
- \* Excessive administration of Normal saline can lead to metabolic acidosis

**GIT High-Yield Points** 



Blood sugar level which produces vagal stimulation: 45mg/dl

The gas present in the fundus of the stomach is mostly due to: Swallowing

Gas within the colon is primarily derived from: Fermentation of undigested oligosaccharides

by bacteria

Hypokalemic metabolic acidosis occurs with excess fluid loss from: Colon

Sodium is absorbed by colonic epithelium by active transport and potassium is excreted into

the colonic lumen passively

The Most common Primary Malignant bone tumor-------Multiple Myeloma

- Commonest true benign tumor-----Osteoid osteoma
- Most common tumor associated with hyperglycemia-----Chondrosarcoma
- Most common tumor causing pulmonary metastasis—Osteosarcoma >> Ewing sarcoma
- Codman's triangle is most commonly associated with----Osteosarcoma
- Onion Peel appearance is most common seen in------ Ewing sarcoma
- Most common cause of pathological fracture is---Osteoporosis>>> metastasis
- The most important factor considered in the prognosis of malignant soft tissue tumors is: Histological grading of primary lesion (Not staging but grading)
- The most common bacteria implicated in bone and joint overall is——Staphylococcus aureus
- Best Radiological investigation for bone infection is MRI>>>Bone scan
- Bone and Joint infection Gold standard is always——Culture and Sensitivity (C/S)

#### **Genetic Disorder**

- Type of inheritance in MELAS: mitochondrial
- Angelman syndrome is due to: Uniparental disomy
- Type of inheritance in tuberous sclerosis: autosomal dominant
- ❖ Gene involved in RETT syndrome: MECP2
- "Frog eye" appearance on USG in second trimester of pregnancy is a features of anencephaly
- Li Fraumeni Syndrome is due to mutation in gene: P53
- \* BRCA-1 Gene is located on: Chromosome 17
- \* Example of Point mutation: Sickle cell anemia
- Klippel Feil Syndrome: Congenital fusion of cervical vertebra. Autosomal dominant inheritance –C2-C3 fusion and Autosomal recessive inheritance- C5-C6 fusion
  - · FEIL'S Triad :
    - ✓ Low posterior hair line
    - ✓ Short neck
    - ✓ Limitation of head and neck movement/decreased range of motion in cervical spine

#### Chapter 31

## Naseem Sherzad High-Yield Points

## Bleeding and Coagulation Disorders

- Defect in Intrinsic Pathway of clotting causes Increase in: aPTT
- Defect in Extrinsic Pathway of clotting causes Increase in: PT
- The best screening test for hemophilia is: APTT
- Increased in vitamin K deficiency: PT
- Von willebrand disease: increase in BT and APTT (Platelet count and PT normal)
- \* Bernard Soulier disease is a defect in: Platelets adhesion (Large Platelets, low count)
- Glanzmann's thrombasthenia: Failure of aggregation (Normal size platelets, normal count)
- \* vWF is useful in: Platelets adhesion to the vessels wall (Normal platelets count)
- · Patient on Aspirin: Prolonged BT
- The most common cause of DIC is: Obstetric complications
- The reason why hemophilia is more commonly observed in human males more than in female is due to: The disease is due to X-Linked recessive mutation
- : Idiopathic Thrombocytopenia Purpura (ITP)
  - Antibody to platelets (antibodies bind to the GPIIb/IIIa receptors)
  - Low platelets count---Most useful test is to check Platelet count
  - BT increase and CT normal
  - Treatment of ITP:
    - ✓ First line treatment: Steroid,
    - ✓ If two relapses with steroid or persistent low platelets or ITP that has persist
      for >6-9 months then splenectomy
    - ✓ Intravenous immunoglobulin: MOA: bind with FC receptors on macrophage
- Thrombotic Thrombocytopenia Purpura (TTP):
  - Rare blood disorder characterized by clotting in small blood vessels, resulting in low platelet counts
  - Consist of Pentad: Microangiopathic hemolytic anemia, thrombocytopenic purpura, severe neurologic abnormalities, fever and renal disease
  - Platelets transfusion is contraindicated in TTP, Hemolytic Uremic Syndrome (HUS) and Heparin Induced Thrombocytopenia (HIT)
- · Hemophilia A:
  - Represent 80% of all hemophilia
  - o Factor 8 deficiency
  - X-linked recessive disorder
  - Normal PT, Elevated aPTT
- Hemophilia B:
  - Also known as Christmas disease
  - Factor 9 deficiency
  - X-linked disorder
  - Normal PT, Elevated aPTT

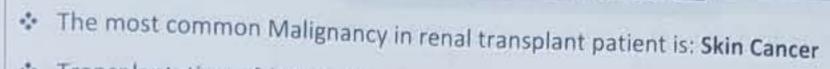
Hemophilia C: Factor 11 deficiency

Chapter 31

#### **High-Yield Points**

- Sever Hemophilia A: Desmopressin + Aminocaproic acid >>>Transfusion of factor 8 to 30% of normal factor level >>> cryoprecipitate. Best Investigation: Factor 8>>> APTT. Example, you are asked to consult on a newborn baby of life 2 due to excessive bleeding after circumcision. The APTT is prolonged and PT is normal. You will order factor assay to diagnosis the cases: answer: Factor 8
- Mild Hemophilia A: Desmopressin alone
- \* Patient Pre-op Pt/Aptt is increased what to give: Desmopressin >>>Cryoprecipitate
- Cryoprecipitate has no role in massive transfusion/coagulation
- · Patient starts bleeding form cannula site after massive transfusion (after transfusion of 10 pint of RBC), the cause of bleeding is dilution thrombocytopenia and treatment is FFP
- . Bleeding during surgery but PT/APTT and Platelets counts are, cause would be: hypothermic coagulopathy
- If pre-Op FFP is needed for minimizing the risk of bleeding due to surgery, Optimal timing is: on call to surgery
- \* Von-Willebrand disease: Desmopressin (Vasopressin analogue)>> Cryoprecipitate
- \* After Massive blood transfusion: FFP and platelets is administered
- \* Transfusion reaction occur with: Donor cell and recipient serum
- . Cross match for Transplant: Donor lymphocyte and recipient serum and compliment
- . Most common cause of transfusion related death is transfusion-related acute lung injury
- \* Bleeding following massive transfusion can occur due to hypothermia, Dilutional coagulopathy, platelet dysfunction, fibrinolysis or hypofibrinogenemia
- Whole blood is effective as a replacement fluid in acute blood loss
- Most common blood produce which is the source of contamination is platelets
- Hemophilia is due to lack of AHF, factor 8 is also known as anti-hemophilic factor or AHF

#### Transplantation



- Transplantation of kidney from mother to son or from sister to brother is an example of: Allograft
- . Highest chance of success in renal transplant patient is seen when the donor is the: identical twins
- A principal cause of death in renal transplant patient is: infection
- The commonest complication of immunosuppressant is: infection
- A Patient has undergone a kidney transplant and on first day, he was unable to produce urine and there is tenderness at transplant site, It is due to: Thrombus at the site of Transplant. Explanation
  - Renal vein thrombosis: It is more common and present early- first week of transplant.
  - Renal artery stenosis: It is less common then renal vein thrombosis and it present late---year after transplant
- For successful transplantation how many HLA should be matched: 5-10
- \* "000" mismatch in graft transplantation means: Matched
- \* HLA DP require minimum matching for Transplantation
- \* HLA-1 is Present on all nucleated cell
- Most common antigen initiating graft rejection is HLA antigen and MHC molecules

#### **Glutamine**

- Fuel for colonocyte: Short chain fatty acid
- Glutamine is the most common Amino acid in blood stream and tissue
- Supplemental Paracentral glutamine should be administered in nutrition probably in all critically ill Patient
- Fuel for enterocytes: Glutamine
- Fuel for most of the Neoplastic cell is: Glutamine
- \* The amino acid producing ammonia in kidney is: Glutamine
- In brain, Asterocytes convert glutamate to glutamine

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Naseem Sherzad High-Yield Points

## Familial Dyslipidemias

Dyslipidemia	Protein defect	Elevated lipoproteins	Major Manifestation
Familial Chylomicronemia Syndrome  (Type 1 Hyperlipoproteinemia)	<ul> <li>Lipoprotein lipase</li> </ul>	Chylomicrons,	<ul> <li>Eruptive sk</li> </ul>
	OR ApoC-II	Cholesterol	<ul> <li>xanthomas</li> <li>Hepatosplenomega</li> </ul>
Familial Hypercholesterolemia (FH)	<ul><li>Deficient</li><li>LDL</li></ul>	LDL,	Premature corona     artery disease  Corpostareus
Familial Hyperlipoproteinemia type 2	receptors  ApoB-100	Cholesteror	<ul> <li>Corneal arcus</li> <li>Tendon xanthoma</li> <li>Xanthelasmas</li> </ul>
Familial Dysbetalipoproteinemia  (Type III Hyperlipoproteinemia)	* ApoE	Chylomicrons and VLDL remnants	<ul> <li>Premature coronary artery disease &amp; peripheral vascular disease</li> <li>Tuboeruptive &amp; palmar xanthomas</li> </ul>
Familial Hypertriglyceridemia  (Type IV familial dyslipidemia)	• ApoA-V	VLDL, TG	<ul> <li>Increase pancreatition</li> <li>risk</li> <li>Associated with obesity &amp; insuling</li> </ul>

## Lungs Development

lungs is derived from ectoderm, while the mesoderm is the origin of pulmonary blood vessels, smooth muscle, cartilage and other connective tissue

Initially lung bud form from the distal end of respiratory diverticulum during week 4. Rest of the development occur in 5 stages.

development occur in 5 stages.	
Embryonic (week 4-7)	<ul> <li>Lung bud formation plus trachea and bronchi differentiation.</li> <li>Errors at the stage lead to tracheoesophageal Fistula.</li> <li>Vascularity in lung is first seen in this stage</li> </ul>
Pseudo glandular (week 5-17)	<ul> <li>Formation of conducting airways, terminal bronchioles surrounded by modest capillary network</li> <li>At this stage, as there are no alveoli, there is no gas exchange – and so the lungs are unable to oxygenate blood.</li> </ul>
Canalicular (week 16-25)	<ul> <li>Terminal bronchioles differentiate in to respiratory bronchioles and alveolar duct. Surrounded by prominent capillary network.</li> <li>Aeration first occurs during this stage. At 25 weeks gestation the fetus is capable of respirations</li> <li>Formation of air-blood interface</li> <li>Pneumocytes development start at 20 week</li> </ul>
Saccular (week 26-birth)	<ul> <li>❖ Alveolar ducts –terminal sacs.</li> <li>❖ ECM formation</li> <li>❖ Surfactant detectable in amniotic fluid</li> </ul>
Alveolar phase (36 week -8 years)	Mature alveoli formation and proliferation and expansion of capillaries, nerve and gas exchange areas

**Insular Cortex** 

Postcentral gyrus

Precentral gyrus

Prefrontal cortex

#### Coxsackievirus

- RNA virus from Picornaviruses family, which is non-enveloped, Single stranded, linear virus.
- Suckling mice are used for coxsackievirus
- Disease caused by Coxsackievirus:
  - Herpangina: Coxsackie B3
  - Myocarditis and pericarditis: Coxsackie B3
  - Hand-foot-and-mouth disease: Coxsackievirus A16 and Entero-virus 71
  - Pleurodynia: Coxsackie B virus
  - Viral meningitis

#### **Virology High-Yield Points**

- Human Papillomatosis is caused by: HPV
- Flat warts care caused by which type HP Virus: 3, 10
- Most common type of HPV associated with cervical cancer: 16, 18
- Condylomata acuminate is caused by: HPV
- . HPV infects which cells first: Basal cell
- Bivalent HPV vaccine contain: Type 16 and 18
- \* Which viral gene acts as a carcinogens in causing carcinoma cervix: E-gene
- \* HPV causes which changes in cervical epithelial: immortalization of epithelial cells
- Low Risk type of HPV: Type-6
- \* Albert staining technique chiefly used to demonstrate Metachromatic granules found in corynebacterium diphtheria.

#### Neoplasia

- \* A Simple bacterial test to mutagenic carcinogen is: Ames test
- Most common cancer, affecting both males and females of the world is: Lung cancer
- \* Reversible loss of polarity with an abnormality in size and shape of cell is known as: Dysplasia
- . How would you differentiate Ca in situ from invasive Ca: Penetration of basement membrane
- Carcinoma which is familial: Breast Carcinoma
- The most common gene involved in endometrial Ca is: PTEN
- K-RAS Protoncogens is associated with: Colon cancer
- Most common inherited malignancy: Retinoblastoma
- BRAF mutation is seen: Melanoma
- "Gatekeeper" of Colonic neoplasia: APC
- \* Hallmark mechanism of tumor suppressor gene inactivation: Loss of heterozygosity

	831.5
Motor apraxia	Difficulty planning motor activity. Due to lesion in Area (5,7)- posterior parietal lobe or due to direct lesion in Premotor area (6)
Somatosensory association	lesion lead to contralateral agnosia and spatial neglect plus loss
cortex	of tactile localization and two point discrimination
	Inability to recognize faces.
Prosopagnosia	Prosopagnosia is also known as face blindness or facial agnosia
	Its Due to lesion in occipital and temporal lobes or inferior
	temporal lobe and fusiform gyrus of temporal lobe

Area for shame, regret, disgust

lesion lead to sensory loss

Lesion lead to motor loss

Higher intellectual functions

**CNS High-Yield Points** 

- \* Tumor spread from infratemporal fossa to middle cranial fossa via: greater wing of sphenoid
- \* Dysphagia is the typical features of: Lateral Medullary syndrome
- \* The largest part of the cerebellum is: middle lobe
- Medial lemniscus is formed by: internal arcuate fibers
- \* Red nucleus is situated at the level of: Mid brain-superior colliculus
- Olivary nucleus is situated at the level of: Medulla
- ♣ Lateral Geniculate body is part of: Thalamus
- \* Precentral gyrus and corticospinal tract are essential for: voluntary movement
- The principle that is spinal cord dorsal root are sensory and ventral root are motor is known is known as: Bell-Magendie's law

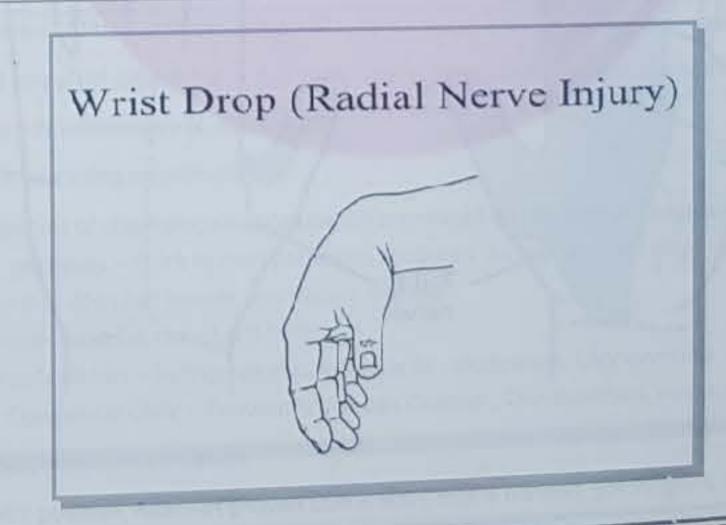
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Naseem Sherzad High-Yield Points

# Correlation Between level of Disk Herniation and the Root Affected

Level of Herniation	Root Affected
L1-L2	L2
L2-L3	L3
L3-L4	L4
L4-L5	L5
L5-S1	S1

<b></b>	Radial Nerve
Injury in Axilla or Proximal humerus	Wrist drop and Finger drop  Loss of sensation over the lateral and posterior arm, posterior forearm and dorsal surfaced of the lateral three and a half digits
In distal humerus/head of radius bone	Wrist drop and Finger drop  No sensory loss
At the level of Wrist	No wrist drop, no finger drop and no motor loss  Sensory Loss: Loss of sensation over radial/Lateral three and half finger, thenar pad and thumb web



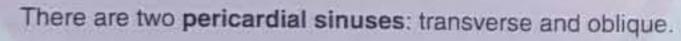
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Precentral Central Postcentral gyrus

FRONTAL LOBE

PARIETAL LOBE

#### **Pericardial Sinus**

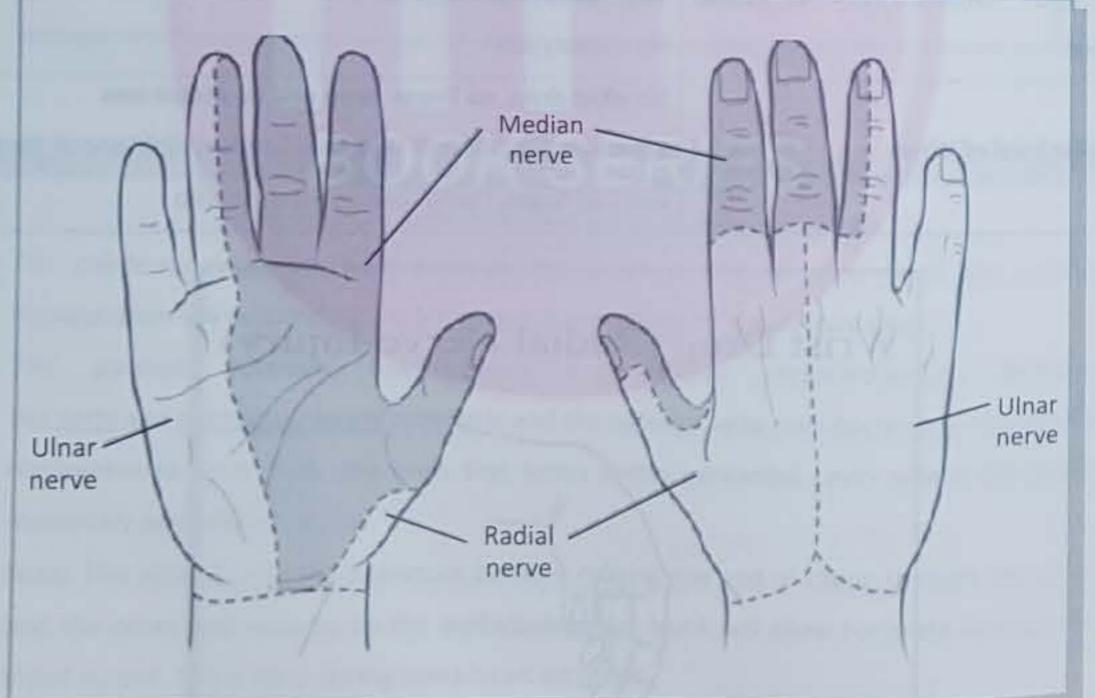


- The cul-de-sac sinus, enclosed between the limbs of the inverted U of the venous mesocardium lies posterior to the left atrium and is known as the oblique sinus.
- The passage between the venous and arterial mesocardia—i.e., between the <u>aorta</u> and <u>pulmonary artery</u> anteriorly and the superior vena cava posteriorly —is termed the transverse sinus. Also, the sinus that forms in the pericardial cavity where the dorsomesentary pericardium reside.
- Note: This sinus is clinically important because passing one end of clamp through the sinus, and the other end anterior to the aorta/pulmonary trunk will allow complete blockage of blood output. This is done during some heart surgeries.
- It can be used to pass ligature during cardiac surgery.

#### Chapter 31

Naseem Sherzad High-Yield Points

····	Ulnar Nerve	·	Microbiology High-Yield Po
Injury at the level of elbow/Medial Epicondyle (Cubital tunnel syndrome)	Radial deviation of the wrist/ Clawing less in 3rd and 4th digits. There will be no complete paralysis of 3rd and 4th digits.	Anthrax	<ul> <li>First anthrax vaccine developed in 1</li> <li>Ascoli's thermoprecipition test had diagnosis of anthrax</li> <li>McFadyean's reaction is employed anthrax</li> </ul>
At the level of Wrist	Wasting and paralysis of intrinsic hand muscle (Claw hand/ intrinsic minus hand), wasting and paralysis of hypothenar muscles/ loss of sensation of medial 1 and half fingers up to the nail beds		<ul> <li>Culture: Blood culture</li> <li>Stain: Sudan</li> <li>It is also known as Clostridium w</li> <li>Cause damage to zona occludes</li> </ul>
Ulnar Paradox	"More proximal level of transection the hand will typically not have a claw like appearance that may be seen following a more distal injury"  Low ulnar nerve palsy is characterized by claw hand	Clostridium Perfringens	<ul> <li>Cause cell injury by inhibiting Gly</li> <li>CLOSTRIDIUM PERFRINGENS information cellulitis of the subcutaneous TIS</li> <li>Boxcar appearance is seen in Control of the Subcutaneous TIS</li> <li>Non-motile Clostridia</li> </ul>
000			❖ Sample of choice for the diagnos



	Microbiology High-Yield Points
Anthrax	<ul> <li>First anthrax vaccine developed in 1881</li> <li>Ascoli's thermoprecipition test helps in confirming the laborator</li> </ul>
	<ul> <li>diagnosis of anthrax</li> <li>McFadyean's reaction is employed for the presumptive diagnosis of anthrax</li> </ul>
	<ul> <li>Culture: Blood culture</li> <li>Stain: Sudan</li> </ul>
Clostridium Perfringens	<ul> <li>It is also known as Clostridium welchii</li> <li>Cause damage to zona occludes (tight junction)</li> <li>Cause cell injury by inhibiting Glycolysis</li> <li>CLOSTRIDIUM PERFRINGENS infection can CAUSE a crepitant cellulitis of the subcutaneous TISSUE</li> <li>Boxcar appearance is seen in Clostridium Perfringens</li> <li>Non-motile Clostridia</li> </ul>
Clostridium Botulinum	<ul> <li>Sample of choice for the diagnosis of botulism is stool</li> <li>Botulism toxin causes Parasympatholytic</li> <li>Death occurs due to respiratory paralysis/failure</li> <li>Botulism is due to Trypsin activates the protoxin to active form</li> </ul>

- Infective endocarditis artificial valve > 60 years staph aureus , <60 years epidermidis
- 4 years old boy after splenectomy due to ITP, most common organism causing infection strept pneumonia > H.influenzae> N. meningitis
- Proteus has swarming movement
- Different species of staphylococcus can be differentiated on the basis of coagulase test
- ❖ Bordetella pertussis strict human pathogen , cultured during Catarrhal stage prevented by cellular vaccine- does not invade respiratory mucosa
- Toxoplasmosis- increase risk of still birth
- Triad of toxoplasmosis hydrocephalus, intracranial calcification, Chorioretinitis
- Pentad for Congenital CMV Periventricular calcification, Chorioretinitis, microcephaly, sensor neuronal loss, mental retardation
- Patient is HIV positive, AIDs not proven CD4 is 800 (that is normal), got Pyogenic otitis media –

- organismis responsible staph aureus
- Granulomatous inflammations not caused by anaerobes
- . Chlamydia trachomatis serovars A-C infect conjunctival epithelial cells and untreated infection can lead to blindness.
- A triad of absolute neutropenia, sinus bradycardia and Hepatosplenomegaly is indicative of Typhoid
- Pseudomonas aeruginosa is present in normal flora of oropharynx
- The initial drug of choice of influenza virus is oseltamivir.
- Otitis media in AIDS- streptococcus pneumonia
- Tubo ovarian abscess gonococcus
- Tubo ovarian abscess with IUCD actinomycosis
- \* CMV signs of meningeal irritation + organism has halo around it
- Paul-Bunnell test: used to screen for Infectious mononucleosis
- Tetanus in population can be prevented by gibing tetanus toxoid
- Stap aureus is the most common bacterial opportunistic infection
- The test to diagnose if patient having shingles is to perform PCR of vesicle fluid
- Corynebacterium Diphtheria:
  - Club shaped bacilli
  - The most likely features is exotoxin which is having serious effect on heart
  - Palisade pattern
  - Chinese letter arranged at acute angle

#### \* AIDS:

- Chorioretinitis in AIDs CMV
- Start retro-viral therapy when CD4 count is less than 350 x 10<sup>6</sup> /L
- Contains reverse transcriptase enzyme
- Transmission mother to fetus
- Atypical lymphocytes + maculopapular rash HIV sero-conversion
- Diseases caused by HPV:
  - warts (6,11)
  - Cervical cancer (16,18)
  - Oropharyngeal carcinoma
  - History of warty growth on vulva HPV (6,11)
  - Mild dysplasia on pap smear HPV cervical cancer (16,18)
- Schick test, developed in 1913, is a skin test used to determine whether or not a person is susceptible to diphtheria.
  - Positive susceptible to diphtheria
  - Negative-immune to diphtheria
  - Pseudo positive-Immune and hypersensitive

Bone disease Ca\*\* Phosphate Alkaline Phosphatase Osteoporosis Normal Normal Normal Osteomalacia Paget's disease Normal Normal Myeloma 1, Normal Normal 1 1, Normal Bone Metastasis ↓, Normal 1° Hyperparathyroidism 1 Normal, 个 Hypoparathyridssssism V 1 Normal Normal, ↑ Renal failure 1

Naseem Sherzad Hi h-Yield Points

#### PHARMACOLOGY

#### Lidocaine:

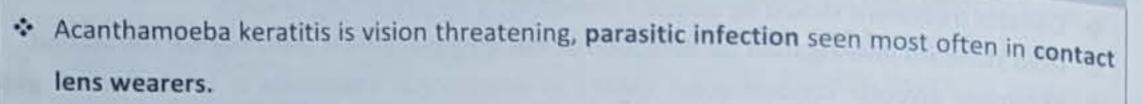
- Maximum safe dose of Lidocaine with epinephrine is 7mg/Kg and without epinephrine maximum safe doses is 4.5mg/kg (For 70 Kg maximum safe dose with epinephrine is 7 x 70 = 490 mg and without epinephrine: 4.5 x 70 = 315mg)
- 2% Lidocaine vial contain: 200mg/20ml means 20mg/ml
- · Rational drug model trail was invented for Alteplase
- Sublingual nitroglycerine is absorbed readily into sublingual vein
- The common side effect of an anti-hyperlipidemia drug is GI disturbance
- Drug bind to albumin remain inactive until activated by liver
- Sulfonamide is the Drug of choice for Nocardia
- · Paclitaxel is chemotherapy drugs which interferes with the normal function of microtubule growth
- Glycopyrrolate is preferred over atropine as Glycopyrrolate does not cross the blood-brain barrier or the placenta
- Altretamine, also known as hexamethylmelamine, is used for the treatment of ovarian cancer is an alkylating agent for which the rout of administration is intramuscular (I/M)
- Suxamethonium is contraindicated in burn patient
- The second-line anti-TB drugs associated with hypothyroidism include ethionamide, prothionamide, and PAS

#### Naseem Sherzad FCPS High-Yield Points

- Grading: Grading of cancer is based on degree of differentiation of the tumor cell and, in some cancer, the number of mitosis and the presences of certain architectural features
- Staging: the staging of solid cancer is based on size of the primary lesion, its extent of spread to regional lymph node and the presence or absence of blood borne metastasis
- Primary malignant melanoma of the choroids most commonly metastasis to liver
- Nikolsky sign is positive and IgG and C3 deposition occur in Pemphigus vulgaris
- Thermal diffusion capacity is the transfer of amount of heat and measure the rate of transfer of heat of a substance or material from the hot side to the cold side.
- Primordial germ cell remains dormant after puberty
- in case of fracture of pelvic outlet, ischial tuberosity is not damaged. The inferior surface means the floor of acetabulum is formed by ischium and pubis
- Post vasectomy: Spermatozoa may be present in the first few postoperative day ejaculation, but that is simply emptying process and now the only secretion of the seminal vesical and prostate constitute the seminal fluid which can be ejaculate as before
- \* Before ejaculation sperms are stored in epididymis
- Opportunistic infections commonly occur during the first 6 months after kidney transplant, including cytomegalovirus (CMV) and polyoma viruses.
- An inflammatory marker for ischemic heart disease is CRP
- The final products of carbohydrate digestion is glucose while the final products of carbohydrates metabolism is Pyruvate
- . The saliva after eating dry fruits become predominantly serous
- Lymph fluid usually contain more than 0.5gm of albumin per 100 ml
- The most common cause of hereditary spherocytosis is Ankyrin
- The most severe form of hereditary spherocytosis is caused by the mutation of alpha spectrin
- Spectrin, Ankyrin and band 4.2 are involved in hereditary spherocytosis
- The biconcave shape of RBC is maintained by membrane protein spectrin
- The most important component in iron hemostasis is the liver-derived peptide hepcidin
- Blood clot contain fibrin

- Antibodies present in hemolytic disease of newborn is anti-A and B
- Danazol treatment should be stopped immediately on deepening of voice
- Gold standard investigation for detection of low lying placenta is trans-vaginal Ultrasound
- Minimum alveolar concentration (MAC) in inhalational anesthesia is related to oil gas coefficient
- Spectrophotometer is based on the Beer-Lambert Law which states that the amount of light absorbed is directly proportional to the concentration of the solute in the solution and thickness of the solution under analysis.
- In a patient of DKA, the most important buffer would be bicarbonate level
- Goose bumps occur due to contraction of Arrector pili (pulling the hairs into an upright position)
- PR segment of ECG coincide with a wave of JVP
- Lymphatic obstruction is caused by combination of infection and neoplasia
- \* The difference between male and female breast is glandular tissue
- Injury to stomach bed, bleeding is likely to occur from splenic artery
- Sex hormones is at peak at 20-30 year of age
- Garden spade deformity is seen in smith fracture (Malunion may occur with a residual volar displacement or shortening of the distal radius, causing a cosmetic abnormality known as a garden spade deformity.)
- The basal ganglia control saccadic eye movements (saccades) by means of their connection to the superior colliculus (SC).
- Urine smell like of burnt sugar in Maple Syrup Urine Disease (MSUD). Urine, sweat, and even the earwax of people with MSUD will often have a sweet smell similar to maple syrup or burnt sugar.
- Peri renal fat at base of kidney is elaboration of renal fascia
- The oxygen in fetal blood leaving the placenta is 30 mm of Hg
- Destination of rectum is caused by activation of parasympathetic system
- . The two vein running parallel with brachial artery in arm are called venae comitantes
- If the pharyngeal clefts are not obliterated by the 2nd pharyngeal arch, they can persist into adulthood as branchial (pharyngeal) cysts. They are typically located in the lateral aspect of the neck, arising at any point along the anterior border of the sternocleidomastoid muscle.
- Brain autopsy of Alzheimer patient will shows atrophy
- Acute tonsillitis:
  - Viral: (50 to 80% of cases): adenovirus, EBV,CMV, HSV, rhinovirus, influenza and parainfluenza
  - Bacterial ((15 to 30% of cases): Generally caused by <u>Group A beta-hemolytic</u> streptococci also known as streptococcus pyoqens (Most common)

#### OPHTHALMOLOGY



- Bilateral left superior quadrantanopia occur due to lesion in right meyer loop. A lesion in Meyer's loop causes a contralateral homonymous superior quadrantanopia, sometimes termed a "pie-in-the-sky" defect.
- Fat pad in the upper eye lid is anterior to levator aponeurosis
- Anterior segment is the front third of the eye that include the structure in front of the vitreous humour: The cornea, iris, ciliary body and lens within the anterior segment, there are two fluid filled spaces:
  - a) Anterior Chamber: The anterior chamber located between the posterior surface of the cornea and (corneal endothelium) and the Iris. Volume of Anterior Chamber is 250 microliters. A hyphema is an accumulation of blood in the anterior chamber of the eye
  - b) Posterior chamber: Posterior chamber is located between the Iris and the front face of the vitreous. Volume of Posterior Chamber is 60 microliters.
- The Posterior segment of the eye comprises the back two third of the eye including the vitreous humor, the retina, the choroid and the optic nerve
- The most common organism causing bacterial conductivities is Stap aureus and Chlamydia common in postnatal conjunctivitis. The common organism involved in Hyperacute conjunctivitis is Neisseria gonorrhoeae
- The best test for Chlamydia trachomatis is serological assays.
- The visual pigment of rod is Rhodopsin (Opsin + 11-cis retinal)
- · Visual impulse (light phase) cause breakdown of Rhodopsin into Opsin plus All-trans retinal
- During dark phase all All-trans retinal converts to 11-cis retinal form, which combine with Opsin and regenerate Rhodopsin.

#### MEDICAL ETHICS

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#### DR-MNS

Set of moral principles, beliefs and values that guide us in making choices about medical care.

- Doctor-Patient relationship the first and foremost is mutual interest
- A breach of confidentiality occurs when a patient's private information is disclosed to a third party without their consent. The confidentiality of the patient can only be breached if the patient allow you or only if the patient is having HIV or STDs because these condition can harm third party
- Information care session is to clear the myths and misconceptions (to remove myths about the disease) of the patient and relative about the disease
- in Emergency department only patient should be allowed into ER room, family and relative should stay outside
- Justice/equity in ethics means fair and equal distribution of health resources
- The foremost part of hippocratic oath is confidentiality
- Referral system: It means sending the patient to a better higher facility with aim of better management of patient
- A doctor provide better management to patient by better communication with patient and active listening and good doctor is known by his pleasant behavior, politeness and bedside manners
- When Then there are two option for treatment, Go with one the patient wants
- To prevent complication of a procedure/intervention, doctor should not cross his competency level
- Seductive females comes to your clinic office, the first step you should to do is to call the nurse
- The professionalism of doctor can be best assessed by recording his or her punctuality, conscientiousness, integrity and availability to patient
- Best approach to the patient should be starting the conversion by asking his name, age etc.
- The urgent concern of the patient when meet with doctor is "what's wrong with him"
- Patient support in our couture is via family
- Type-A personality is at risk of increase heart disease

Naseem Sherzad High-Yield Points

## Naseem Sherzad FCPS High-Yield Points

- Houston's valves or the valves of Houston are semi-lunar transverse folds of the rectal wall that protrude into the rectum, which disappear after mobilization of the rectum
- The jejunum has a thicker wall and a wider lumen than the ileum and mainly occupies the left upper and central abdomen. Mesenetric fat is less in jejunum
- Vaccine for post-splenectomy: Pneumococcal and meningococcal (given At least 2 weak prior to surgery or 2 week after surgery in emergency splenectomy, which is the most effective prevention strategy against OPSI)
- Muscle relaxant of choice in hepatic and renal failure Cisatracurium
- · Vitamin-D resistant rickets found with Fanconi syndrome
- The fundamental cause of erythroblastosis fetalis is hemolysis of Rh-positive fetal RBCs by maternal anti-D IgG antibody
- In the ovaries, aromatase is located primarily in the granulosa cells (GC) of the follicle
- Fat embolism: It can be identified using formalin-fixed tissue with fat stains on frozen sections. Dx: Fat in urine and initial treatment is heparin
- Accommodation reflex is normal and pupillary reflex (light reflex) is absent in condition like encephalitis, diabetic neuropathy and multiple sclerosis
- Calorie restriction (CR) is an effective strategy to delay the onset and progression of aging phenotypes in a variety of organisms.
- · Protein breakdown is increased in skeletal muscle injury
- Frank-Starling law of the heart: The law states that the stroke volume of the heart increases in response to an increase in the volume of blood in the ventricles, before contraction (the end diastolic volume), when all other factors remain constant
- Laplace law: the pressure (P) in a bubble is equal to 4 times the surface tension (T) divided by the radius (r). As applied to the grape-like alveolus, where only the inner wall has a liquid surface exposed to gas, the formula is P = 2T/r.
- \* Boyle's law is a gas law which states that the pressure exerted by a gas (of a given mass, kept at a constant temperature) is inversely proportional to the volume occupied by it. In other words, the pressure and volume of a gas are inversely proportional to each other as long as the temperature and the quantity of gas are kept constant.
- The bleeding tendency in case of obstructive jaundice is due to a prothrombin deficiency.
- There are four main clinical variants of basal cell carcinoma. These are nodular, superficial spreading, sclerosing and pigmented basal cell carcinomas. Nodular is the most common type. Most common site of BCC is head and neck. Most common site in face is nose
- ❖ Phrenic nerve: Correlate with page No.38 and 49
  - Motor supply of the diaphragm on each side is by the phrenic nerve
  - Avulsion of the phrenic nerve in at origin cause paralysis of the corresponding half of the diaphragm

#### Capillaries:

- There are 3 types of capillary in the body; fenestrated, continuous and sinusoidal
- Fenestrated: These capillaries can be found in tissues where a large amount of molecular exchange occurs, such as the kidneys, endocrine glands, and small intestine. They are particularly important in the glomeruli of the kidneys
- Continues: Continuous capillaries are generally found in the nervous system, as well as
  in fat and muscle tissue.
- Sinusoidal capillaries are mainly found in the liver, between epithelial cells and hepatocytes.

#### · Arches of the foot

- The main support/structural keystone of lateral longitudinal arch is cuboid.
  - ✓ Posterior pillar of lateral arch: medial tubercle of calcaneum
  - ✓ Anterior pillar of lateral arch : head of lateral two metatarsals
- The main support/structural keystone of medial longitudinal arch is talus. Medial arch
  of foot is made of spring ligament (plantar calcaneonavicular ligament).
  - ✓ Posterior pillar of medial arch: Medial tubercle of calcaneum
  - ✓ Anterior pillar of medial arch : head of medial three metatarsals

#### There are four types of skin melanoma

- ✓ Superficial spreading melanoma is the most common type. It is more commonly found on the arms, legs, chest and back. (nail bed)
- ✓ Nodular melanoma is the second most common type.
- ✓ Lentigo maligna melanoma is less common.
- ✓ Acral lentiginous melanoma is the rarest type. The most common site is the plantar surface of the foot (sole of the foot). Most in Dark skin people

#### **Hypertrophic Scar**

## Extensive scar that does not extend beyond Scar tissue that extends beyond the

- the boundaries of the original incision or wound.
- Collagen type III common in hypertrophic scar and type I common in keloid scar.
- Hypertrophic scar promote scar contractures
- It is Common in post burn injury

#### **Keloid Scar**

- Scar tissue that extends beyond the boundaries of the original incision or wound.
- The worst position for scar (prone for keloid) is sternum.
- Don't promote scar contractures.
- It is common in darkly pigmented skin and having strong familial tendency

#### **Anti-Tuberculosis Drugs**

- \* First line Anti-TB: Isoniazed, Rifampicin, Ethambutol and Pyrazinamide
- 2nd line Anti-TB: Fluoroquinolones, injectable drug (Capreomycin, Kanamycin and amikacin), oral Bacteriostatic second line drug like cycloserine, Thioamides including ethionamide and prothionamide are considered interchangeable second-line Bacteriostatic agents for MDR-TB
- \* Multidrug resistance: Resistance to at least both Isoniazed and Rifampicin
- Poly- resistance: Resistance to more than one first line anti-TB drug, other than both Isoniazed and Rifampicin
- \* Mono-resistance: Resistance to one first line anti-Tb drug only
- Extensive drug resistance: Resistance to any Fluoroquinolones, and at least one of the three second line injectable drug (Capreomycin, Kanamycin and amikacin), in addition to multidrug resistance
- Patient is not responding despite treatment. What could be the cause? Ans: Misdiagnose which could be due to lymphoma or other granulomatous diseases

#### Concept of Crossed and Uncrossed Lesion

- Hemiplegia can result from a unilateral lesion of the brain stem, internal capsule, or cerebral cortex.
- ❖ Brain stem lesions result in crossed hemiplegia. For example, a left pontine lesion will result in left facial weakness of lower motor neuron type and right-sided hemiplegia. Similarly, a lesion in the left midbrain will result in left-sided oculomotor weakness with right hemiparesis and right facial weakness of upper motor neuron type. This constellation of signs is called Weber syndrome.
- Lesions above the level of the brainstem result in uncrossed hemiplegia. For example, a lesion in the left internal capsule would result in right Hemiplegia and right facial weakness of the upper motor neuron type. A left cortical lesion may also result in cortical dysfunction in addition to right hemiparesis and facial weakness of upper motor neuron type

## Naseem Sherzad FCPS High-Yield Points - 2024

- The hepatitis B vaccine is an injection (or shot) that is generally given in the arm (I/M) as a three-dose series on a 0, 1, and 6-month schedule.
- Echinocandin resistance has emerged over the recent years. It has been found in most clinically relevant Candida spp., but is most common in C. glabrata
- Mylasis is a parasitic infection caused by an infestation of fly larvae, also referred to as maggots.
- Brain-Eating Amoeba, Naegleri fowleri is an amoeba that can cause a serious central nervous system infection. N. fowleri is a free-living ameboflagellate found in warm bodies of water such as ponds, irrigation ditches, lakes, coastal waters, and hot springs
- The vasa recta capillaries are long, hairpin-shaped blood vessels that run parallel to the loops of Henle.
- For humans, the entire process of spermatogenesis is variously estimated as taking 64 days
- Familial periodic paralyses are a group of inherited neurological disorders caused by mutations in genes that regulate sodium and calcium channels in nerve cells.
- Around 20-25% of white blood cells are B and T lymphocytes.
- The high amount of calcium found in astronaut's blood during spaceflight (much higher than on Earth) reflects the decrease in bone density, or bone mass.
- Horseshoe kidney is the most common renal fusion anomaly, accounting for 90% of all cases, In 15-20% of cases of horse shoes kidney PUJO and secondary stone occur
- Uterine artery Doppler measurement may be useful in predicting complications of earlyonset pre-eclampsia (<34 weeks' gestation).</p>
- CD8<sup>+</sup>T cells are recruited in the majority as T80 cells (although a small percentage are recruited directly as T8 or TC cells). T80 cells undergo differentiation into T8s and TC cells.
- . Alosetron is a potent and selective antagonist of the serotonin 5-HT 3 receptor type.
- Simvastatin an HMG-CoA reductase inhibitor, acts by decreasing cholesterol synthesis and by increasing low density lipoprotein (LDL) catabolism via increased LDL receptor activity.
- Fenofibrate is used to treat patients with hypertriglyceridemia, primary hypercholesterolemia, or mixed dyslipidemia. It reduces low-density lipoprotein cholesterol (LDL-C), total cholesterol, triglycerides, and apolipoprotein B and increases high-density lipoprotein cholesterol (HDL-C) in adults.
- Exenatide is a GLP-1 agonist used in the management of type 2 diabetes mellitus.
- Acute appendicitis: The inflamed appendix is red, swollen and demonstrates a yellow purulent and fibrinous exudate on the serosal surface.
- Transfusion-related acute lung injury (TRALI) is defined as new acute lung injury (ALI) that occurs during or within six hours of transfusion, not explained by another ALI risk factor.
- The vas deferens consists of an external adventitial sheath containing blood vessels and nerves, a muscular middle layer composed of three layers of smooth muscle (with a circular

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muscle layer interposed between two longitudinal muscle layers), and an internal mucosal lining consisting of pseudostratified columnar epithelium (which bears the nonmotile stereocilia). The vas deferens has the greatest muscle-to-lumen ratio of any hollow organ. The ampulla of vas deferens act as a reservoir for sperm

- . Bulbar palsy refers to a range of different signs and symptoms linked to impairment of function of the glossopharyngeal nerve (CN IX), the vagus nerve (CN X), the accessory nerve (CN XI), and the hypoglossal nerve (CN XII). It is caused by a lower motor neuron lesion in the medulla oblongata, or from lesions to these nerves outside the brainstem, and also botulism. The patient will have dysphagia, dysarthria, flaccid pareses, atrophy and fasciculation of muscles supplied by those cranial nerves and fibrilliation of the tongue. In addition, the patient would have weakness of the palate and reduced or absent gag reflex, dribbling of saliva and a nasal speech.
- The trigeminal nerve (cranial nerve V) sends fibers to the olfactory epithelium to detect caustic chemicals, such as ammonia.
- Choroid plexus papillomas are an uncommon, benign (WHO grade 1) neuroepithelial intraventricular tumor, which can occur in both the pediatric (more common) and adult population. On imaging, these tumors are usually identified in the fourth ventricle in adults and in the lateral ventricles in the pediatric population
- Ectodermal dysplasias are a heterogeneous group of disorders characterized by developmental dystrophies of ectodermal structures. These tissues include the skin, hair, nails, eccrine glands and teeth. Hypohydrotic Ectodermal Dysplasia is the most common type and is usually inherited as an X-linked recessive trait. It is characterised by the triad of signs which comprises of sparse hair (atrichosis or hypotrichosis), abnormal or missing teeth (anodontia or hypodontia), and inability to sweat due to lack of sweat glands (anhidrosis or hypohidrosis).
- Amyotrophic lateral sclerosis (ALS) and lateral sclerosis are both motor neuron diseases, progressive disorders of older people that affect neurons of the ventral horns, of the medullary motor nuclei, and of the corticospinal tracts. ALS, or Lou Gehrig disease, is characterized by muscle wasting due to loss of the ventral-horn cells (the lower motor neurons). Lateral sclerosis is the loss of axons in the lateral columns of the spinal cord (the upper motor neurons of the corticospinal tracts).
- Carotid cavernous fistula (CCF) results from abnormal communication between previously normal carotid artery and cavernous sinus. Patients with CCF may present with pulsatile exophthalmos, chemosis and complaints of hearing a noise/sounds in the head.
- Liver necrosis (whether it appears as ballooning degeneration, apoptotic bodies, or coagulative necrosis) occurs mainly in the centrilobular zones
- . Heuser's membrane (or the exocoelomic membrane) is a short lived combination of hypoblast cells and extracellular matrix.
- ❖ Dapsone induced hemolysis in a patient with Hansen's disease and G6PD deficiency

Naseem Sherzad High-Yield Points

- \* Sneeze reflex: afferent TGN, efferent Vagus nerve
- . Corneal reflex: afferent TGN, efferent Facial nerve
- Gestational age > fundal height (Oligohydramnios:): Renal agenesis
- Gestational age < fundal height (Polyhydramnios:): esophageal atresia</p>
- Extraembryonic Coelom: Epiblast
- Extraembryonic Mesoderm: Endoderm
- Intraembryonic Mesoderm: Lateral Plate Mesoderm
- Left Umbilical vein: ligamentum teres
- Right umbilical vein: obliterates
- Umbilical arteries: Medial umbilical ligament
- Urachus: Median umbilical ligament
- Yellow granules: actinomyces
- Yellow colonies: staph auras
- Stretch reflex: monosynaptic
- Inverse stretch reflex: disynaptic
- Withdrawal reflex: multisynaptic
- Adrenal cortex derived from: Mesoderm
- Adrenal medulla derived from: neural crest

#### **Antidotes**

- Opioids/Morphine-----Naloxone
- Phenobarbital------Bicarbonate (NaHCO3)
- Aspirin------Birarbonate
- · Iron Toxicity------Deferoxamine
- . Heparin-----Protamine sulfate
- ❖ Warfarin and Coumadin-----Vitamin K, FFP use to reverse bleeding in sever overdose
- \* Beta-Blocker-----Glucagon
- ❖ Insulin-----Glucose
- Mushroom poisoning------Atropine
- \* Atropine-----Physostigmine or Pilocarpine
- Diazepam-----Flumazenil
- ❖ Acetaminophen/Paracetamol overdose----- N-acetylcysteine
- Methotrexate cause myelosuppression reversible with ----- Leucovorin "Rescue"

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Naseem Sherzad High-Yield Points

### Penile Ulcer

## Condyloma lata, the flat papule of ----Secondary Syphilis---painless ulcer with Painless Inguinal Lymphadenopathy

- . Chancroid is an STD caused by Haemophilus ducreyi. It is characterized by painful ulcer and Painful Inguinal lymphadenitis (Chancroid, C: Cry, Painful)
- . Lymphogranuloma Venereum caused by Chlamydia----LGVC, Causing Painless ulcer and Painful Inguinal lymphadenitis
- · Granuloma Inguinale caused by Klebsiella (formerly Calymmatobacterium) granulomatis. Characterized by intracellular inclusions in macrophages referred to as Donovan bodies. Painless ulcer, Inguinal lymphadenitis is uncommon
- \* Herpes Simplex: Painful Ulcer

#### **Diagnostic Points**

- . Candida albicans-----Pseudo-Hyphae
- Mucor/Rhizopus-----Non-Hyphae
- Bacterial vaginosis-----Clue cells, Fishy Smell
- \* Trichomonas vaginalis-----Strawberry cervix
- Vulva Intraepithelial Disease/Pre-malignant lesion----Paget Disease
- Most common lesion of vulva------Condyloma acuminata (Genital warts)
- Most common opportunistic infection in HIV-----TB
- Most common opportunistic infection in AIDS------Pneumocystic jivorcii
- ❖ Fungal in HIV------Candida albicans
- Most common opportunistic infection in immunocompromised-----Candida

### Difference Between Anorexia Nervosa and Bulimia Nervosa

#### **Bulimia Nervosa** Anorexia Nervosa Individuals engage in repetitive cycles of A form of self-starvation binge-eating alternating with self-induced Tone of lower esophageal sphincter loss due to Nitric oxide (NO) vomiting or starvation There is impaired glucose tolerance The frequent purging people with bulimia can test in patient of Anorexia nervosa permanently erode the protective enamel · Carries highest mortality rate Common Features: coating on teeth. Amenorrhea Self-perception of being fat Underweight Intense fear of gaining weight

## **Chromosomal Abnormalities**

- \* ARPKD: Mutation of PKHD1 gene on Chromosome 6
- ADPKD: 99% have Mutation either of PKD1 gene on Chromosome 16 or less often of the PKD2 on chromosome 4
- Tuberous sclerosis: Chromosome 9 and 16, Renal Angiomyolipoma are commonly seen in patient with Tuberous sclerosis
- \* Von Hippel-Lindau (VHL): Located on the short arm of chromosome 3, which is affected in more than 90% of clear cell RCC, VHL is associated with Hemangioblastoma, RCC and Pheochromocytoma
- Wilms tumor: WT1, the first Wilms tumor suppressor gene at chromosomal band 11
- Sickle cell disease is caused by a mutation in the hemoglobin-Beta gene found on chromosome 11
- Neuroblastoma Deletion of the short arm of chromosome 1, adverse prognosis
- \* Prostate cancer families has provided evidence of linkage to the long arm of chromosome 1
- Most testicular cancer cells have extra copies of a part of chromosome 12.
- \* Wilson disease is caused by one of the several mutations in ATP7B gene present on chromosome 13
- The retinoblastoma gene (Rb) is a tumor suppressor gene found on chromosome 13.
- PSA is encoded on chromosome 13
- Marfan syndrome is caused by mutations in the FBN1 gene on chromosome 15, which encodes the protein fibrillin-1.
- \* Prader-Willi syndrome is caused by a genetic change on chromosome number 15.
- \* Wiskott Aldrich syndrome: Child with Triad of thrombocytopenia, immunodeficiency & eczema.
- Alport syndrome: Patient with broad nose, Syndactyly, Exophthalmos, cleft palate and dished in face appearance
- \* The Knudson hypothesis, also known as the two-hit hypothesis suggested that two "hits" to DNA were necessary to cause the cancer. In the children with inherited retinoblastoma, the first mutation in what later came to be identified as the RB1 gene, was inherited, the second one acquired. In non-inherited retinoblastoma, instead two mutations, or "hits", had to take place before a tumor could develop, explaining the later onset.

Patient having heart rate (HR) 70 beat/min, Cardiac Output CO: 5.6 L, End-Diastolic Volume (EDV): 160ml, Calculate ejection (EF)?

#### Formula for EF= SV + EDV

We do not have Stroke volume (SV) in given question To calculate SV we use the following formula

Cardiac output (CO)= Stroke volume SV × Heart Rate
To find stroke volume:

Given Value
CO is 5.6 L (5600ml)
EDV is 160ml
HR is 70

SV= CO ÷ HR= 5600ml ÷ 70= 80

So SV is 80

Now for EF:

EF= SV + EDV (80+160=0.5)

EF= 0.5 L

Heart rate is 75 PR interval is 0.3 if heart rate becomes 225 what will be the PR interval?

#### **Explanation:**

Heart rate is inversely proportional to the PR interval so if we increase the heart rate 3 times the PR interval will decrease by 3 times

225/75= 3 0.3/3= 0.1

Calculate embryonic age if Last menstrual period is 15-11-2020 and today is 15-2-2021?

For women who conceive naturally, gestational age is calculated as follows: gestational age is calculated from the first day of menstruation of the last menstrual cycle. Accordingly, the age of the fetus will be 14 days older than the actual age of the fertilized ovum (equivalent to 2 weeks).

Total day from 15-11-2020 to 14-2-2021 = 91 days Now: 91-14 = 77 days which is equal to 11 weeks

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Expected Date of delivery: is 280 days or 40 weeks from LMP

EDD = (LMP - 3months + 7 days) + 1 year

For example: LMP was on 10 August'20

EDD=(10 August'20 - 3 months +7days)+1 year

EDD=(10 may'20 + 7 days) + 1 year

EDD= (17th May'20)+ 1 year

EDD=17th May 2021

Calculate the mean arterial pressure when systolic pressure is 132 and diastolic is 66?

#### Explanation:

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Pulse pressure = Systolic - diastolic

Mean arterial pressure has 2 formulas, Given in detail in CVS Chap of Naseem Sherzad

1- Diastolic pressure - 1/3rd pulse pressure

2- 2/3 diastolic pressure + 1/3rd systolic pressure

So now first we will calculate pulse pressure

PP = systolic - diastolic

PP = 132 - 66

PP = 66

Now

MAP = Diastolic pressure - 1/3rd PP

MAP = 66 + (1/3rd of 66 is 22)

MAP = 66 + 22

MAP = 88

#### By second formula

MAP = 2/3rd diastolic + 1/3rd systolic

MAP = 2/3 (66) + 1/3 (132)

MAP = 44 + 44

MAP = 88 Answer.

A Patient with heart rate of 75 has ventricular systole duration/PR interval of 0.3 sec, at heart rate of 225 the systolic timing/PR interval will be?

a) 1 sec

b) 0.9 sec

- c) 0.05 sec
- d) 0.1 sec
- e) 0.2 sec

#### **Explanation:**

Ventricular systolic duration/PR interval 0.3 sec at heart rate of 75 beat/min

Ventricular systolic duration/PR interval on heart rate of 225 will be?

Increase in heart rate will decrease PR interval so at 225 which three time of normal, the PR interval will be: 0.1 sec

So at heart Rate of 75: PR interval is 0.3-----Inversely related, increase in PR interval would decrease the rapid ejection and heart rate

At heart rate of 150: PR interval will be 0.2

At heart rate of 225: PR interval will be 0.1

Urine concentration is 100 urine flow rate is 2, plasma concentration is 10 calculate the clearance?

Explanation:

Clearance = U × V/p

U= Urine concentration

V= Urine flow rate

P= Plasma concentration

Clearance =  $U \times V/p$ 

Clearance =  $100 \times 2/10$ 

Clearance= 200/10

Clearance= 20 Answer.

Patient Hb is 10, O2 saturation is 90% and Po2 is 60, calculate the Hb content?

A-10

B-13

C-18

D-21

Explanation:

Each gram of O2 carries 1.34 molecule

So if Hb is 10

 $10 \times 1.34 = 13.4$  Answer.

Dopamine exerts its effect when it reached a steady state if it's half life is 2 min after how many minutes it will show it's affect?

A-2 mins

B-4 mins

C-9 mins

D-15 mins

Explanation:

Steady states takes 4-5 half lives to achieve

So 2(Half life of dopamine) × 5 (steady state half life)

2×5= 10 nearest in option is 9 so that is the answer.

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Calculate BMI of a girl when weight is 89 kg and height is 172 cm?

A-27

B-51

C-42

D-52

**Explanation:** 

BMI = weight in kg / height in meter (power 2)

BMI = 89/ (172)2

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BMI = 89 /2.9

BMI = 30 nearest is 27 that is the answer.

If a vial contains 2% of 4 ml lidocaine, how much in mg lidocaine is?

A-8mg

B-80mg

C-20mg

D-200mg

Explanation:

2 % means 2 gram(2000mg) in 100 ml . So after calculation answer is 80 mg

100 ml=2000mg

1ml=2000/100

4ml=2000/100 X 4 = 80 mg Answer.

Calculate the alveolar ventilation rate where tidal volume is 350ml, dead space is 100 ml (norm dead space is 150ml if no value given in question assume that) and Respiratory rate is 18?

**Explanation:** 

Va=Vt - Dead space × RR

Where

Va=Alveolar ventilation

Vt=Tidal volume

Va=350-100 × 18

Va=250 × 18

Va= 4500ml or 4.5L

Calculate Vd/Vt (physiological dead space) when paCo2 is 45 mm hg excreted Alveolar ventilat peCo2 is 30 mm hg?

Vd/Vt = paCO<sub>2</sub> - peCO<sub>2</sub>/paCO<sub>2</sub>

Explanation:

Vd/Vt=paCo2 - peCO2/paCO2

Vd/Vt = 45 - 30/45

Vd/Vt = 15/45

Vd/Vt = 0.3 Answer.

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NASEEM SHERZAD FCPS -1 HIGH-YIELD

Lung volume measured is 6L tidal volume is 0.5 L and amount of air that can be expired after tidal volume is 3.5 I what is the vital capacity?

A-1.51

B-3.51

C-51

D-61

#### **Explanation:**

Tidal volume is normal breathing we do when we do forceful expiration that is Inspiratory reserve volume and forceful expiration we do that is Expiratory reserve volume and amount left after forceful expiration in lung is reserve volume

Normal values of these are

Tidal volume - 0.51

IRV - 11

ERV - 3.5 I

RV - 1.5 |

Vital Capacity (VC) = TV + IRV + ERV

Inspiratory capacity = TV + IRV

Functional residual volume = ERV + RV

Total lung capacity = TV + IRV + ERV + RV

This was the general concept now to solve the above question

Vital capacity = TV + IRV + ERV

Since IRV value is not given we will assume that value that's 1 L so

VC= 0.5l + 1l + 3.5l

VC= 5 | Answer.

Q5.A 35 year old man has a vital capacity of 5 I a tidal volume of 0.5 I an Inspiratory capacity of 3.5 liter a functional residual capacity of 2.5 I what is his expiratory reserve volume?

A-4.51

B-3.51

C-1.51

D-2.51

**Explanation:** 

#### VC = TV + IRV + ERV

Now we will reverse this because except ERV we have all values and when we reverse the + will change into minus

ERV = VC - IRV - TV

ERV = 51 - 3.5 - 0.5

ERV = 1 L nearest in option is 1.5 liter so that is the answer.

Cardiac Cycle

- The contraction of the atria (both the right and left) physiologically precede that of ventricles (both right and left).
- Cardiac cycle events can be divided into diastole and systole. Diastole represents ventri Relaxation/filling, and systole represents ventricular contraction/ejection.
- Atrial systole/Contraction of the atria/depolarization----represented by the P wave of the I
- Ventricular systole/Contraction/depolarization----represented by the QRS complex.
- Ventricular relaxation/ diastole/ depolarization of the ventricles----represented by the T was
- Anatomically the ventricular depolarization (QRS Complex) travels from apex to base and endocardium to epicardium. The wave of repolarization moves in the opposite direction epicardium to endocardium.
- The PR interval is the time from the onset of the P wave (Atrial systole/Contraction of atria/depolarization) to the start of the QRS complex (Ventri systole/Contraction/depolarization). It reflects conduction through the AV node.
- Both ventricles completely depolarized: ST segment
- The QT interval indicates of the time from ventricular depolarization to ventri repolarisation. It reflects the total duration of the ventricular electrical systole.
- The first heart sound is produced by the closing of the mitral and tricuspid valve leaflets second heart sound is produced by the closing of the aortic and pulmonic valve leaflets.

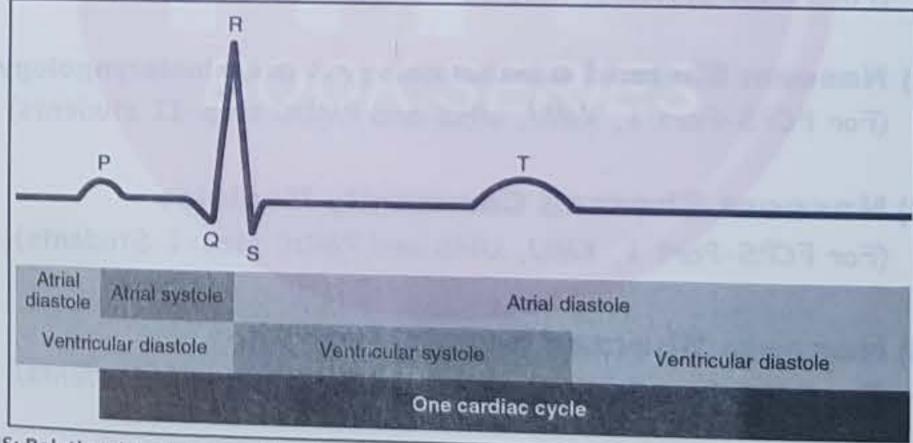


Figure MNS: Relationship between the Cardiac Cycle and ECG Initially, both the atria and ventricle relaxed (diastole). The P wave represents depolarization of the atria and is followed by atrial contra (systole). Atrial systole extends until the QRS complex, at which point, the atria relax. The QRS corresponds depolarization of the ventricles and is followed by ventricular contraction. The T wave represents of all these Wave given of this book Chapter 4. Page # 82

# The END Wishing You All THE BEST

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## My other valuable publications

- 1) Naseem Sherzad House Job Guide
  (For House officers, Medical officers and internees)
- 2) Naseem Sherzad Ophthalmology & Otorhinolaryngology (For FCPS-Part 1, KMU, UHS and PMDC step-II students)
- 3) Naseem Sherzad Community Medicine
  (For FCPS-Part 1, KMU, UHS and PMDC step-1 Students)
- 4) Naseem Sherzad Special Pathology
  (For FCPS-Part 1, KMU, UHS and PMDC step-1 Students)